CHRONOLOGICAL EFFECT ON INSULIN AND GLYCEMIC STATUS IN CANCER PAIN PATIENTS

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
Chennai-600096

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY
IN
PHARMACY PRACTICE

Submitted by
REG. NO: 26105587

Under the Guidance of

Dr. M.P.Narmadha, M .Pharm., Ph.D.,

DEPARTMENT OF PHARMACY PRACTICE

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

ELAYAMPALAYAM

TIRUCHENGODE-637205

TAMILNADU.

MAY -2012

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

Elayampalayam, Tiruchengode, 637205
Namakkal (DT), Tamilnadu.
Phone: 04288-234417(8lines)
Fax: 04288-234417

Dr. M.P.NARMADHA, M. Pharm., Ph.D.,
Principal

CERTIFICATE

This is to certify that the Dissertation entitled **"Chronological effect on insulin and glycemic status in cancer pain patients"** submitted to The TamilNadu Dr. M.G.R. Medical University, Chennai, is a bonafide project work of **Miss. Neenu.B.Niravath (Reg No:26105587),** carried out in the Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Tiruchengode for the partial fulfillment for the degree of Master of Pharmacy under the guidance of **Dr.M.P.NARMADHA, M.Pharm, Ph.D.** Swamy Vivekanandha College of Pharmacy, Tiruchengode. This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

Dr.M.P.NARMADHA M.Pharm, Ph.D

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

Elayampalayam, Tiruchengode, 637205
Namakkal (DT), Tamilnadu.
Phone: 04288-234417(8lines)
Fax: 04288-234417

Dr. N.N.RAJENDRAN, M. Pharm., Ph.D.,
Director of PG Studies and Research

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Dr. N.N.RAJENDRAN M.Pharm., Ph.D.,

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

Elayampalayam, Tiruchengode, 637205
Namakkal (DT), Tamilnadu.
Phone: 04288-234417(8lines)
Fax: 04288-234417

Dr. M.P.NARMADHA, M.Pharm., Ph.D.,
H.O.D., Department of Pharmacy Practice

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Dr. M.P.NARMADHA M .Pharm., Ph. D.,

ACKNOWLEDGEMENT

First and foremost I bow down before **Lord Almighty** for his splendid blessings and care in completing my project work and throughout my life till this very second.

I render my sincere thanks to our Honorable Chairman and Secretary, **Vidhya Ratna, Rashtriya Ratna, Hind Ratna Thiru Dr.M.Karunanidhi, M.S., Ph.D, D.Litt**. for providing all facilities for my studies and rendering his noble hand in the upliftment of woman education in all the disciplines.

It is difficult to overstate my gratitude to my guide, **Dr.M.P.Narmadha , M.Pharm, Ph.D.,** Principal of this institution and Head of Pharmacy Practice department. Her enthusiasm and integral view on research and her mission for providing only high-quality work and not less, has made a deep impression on me. I owe her lots of gratitude for having me shown this way of research.

It is my privilege to submit the profound sense of gratitude and respectful regard to our esteemed, **Dr.N.N.Rajendran M.Pharm., Ph.D., Director of P.G. studies &research**, Swamy Vivekanandha College of Pharmacy,for his valuable suggestions, remarkable guidance and constant encouragement. His vast knowledge, his attitude of research and skill of presentation have been an invaluable resources to me.

I wish to express my warm and sincere thanks to assistant professor Department of Pharmacology **Mr. B.Nandha Kumar., M. Pharm., (Ph.D).,** Thanks for his willingness to offer continuous guidance, support and encouragement, which are driving forces for me to complete this thesis. His vast knowledge, his attitude of research has been an invaluable resource to me. He is an admirable professor and will always be a role model for me.

I would also like to express my heartfelt thanks to lecturer Mr.A.Palanisamy, M.Pharm,(Ph.D), for his guidance, encouragement and advice in completing this work.

I sincerely express my gratefulness to **Dr. K. Velavan, MD,RT** for permitting me to carry out this project in his hospital, Erode. Also his valuable and important advises encouragement which gave me confidence to carry out this project successfully.

I take this opportunity to tell my special thanks to **Dr.Moorthy**, **Miss.Remya** for their help and support in all my laboratory tests and procedures. I also like to thank our lab assistant **Mrs. Poomkudi** for her help during my project work

I owe my sincere thanks to my **Parents and brother** who supported and encouraged me during this work.

Friends are treasures to me and it is very difficult to overstate my thanks to all my friends and colleagues .I wish to extend my warmest thanks to all my friends for their support in all times of need. I express my sincere thanks to **Divya, Anisha**, **Alinda, Abdu, Jithin, Arifa, Usha, Ancy, Yemshy, Deepa** for rendering their friendly support during my thesis work.

I also take this opportunity to express my sincere thanks to all my patients who co-operated and helped me in this project to make this a successful one.

I fell delighted to express my whole hearted gratitude to all those who gave their helping hands in completing my course and my project successfully

Neenu.B.Niravath

Reg.No:26105587

CONTENTS

ABSTRACT

1. ABSTRACT

Pain is the first sign of malignancy and prevalent symptom experienced by cancer patients. Circadian rhythm is the best known and probably most general rhythm in living creatures. It plays a very important role in the pattern of pain produced by various diseases. Time dependent variation affects perception of pain, its neurochemistry, and drug treatment. Endogenous insulin plays a critical role in the modulation of pain has been documented in clinical and preclinical studies. The aim of this study was to determine the insulin's antinociceptive effect and also to study the influence of circadian rhythm on cancer pain. This study was done in Erode Cancer centre, Erode wherein we recruited 22 patients for the study. Patients were categorized as Group A, Group B, Group C. Group A included patients taking opiod drugs, Group B-patient taking nonopiods and Group C control patients without pain. Pain was assessed in patients using Visual Analogue Scale. Blood samples were collected from patients four times a day (6AM, 12PM, 6PM, 12AM)with their consent. Serum Insulin level were determined by ELISA method using DRG INSULIN KIT. Results were analyzed using computerized statistical package of Graphpad Instat Software. The statistical significance was tested by the analysis of variance(ANOVA) and Tukey - Kramer Multiple Comparisons Test. In opioid taking patients serum insulin level showed a increase in morning 6AM(31.3125±20.812) and afternoon 12PM (33.05±12.757). Whereas in nonopioid taking group increase in insulin level was found at evening 6PM (69.1875±21.290) and midnight 12AM(67.337±30.728). The serum insulin level in opioid and nonopioiod taking patients was increased and found highly significant(p value<0.0001) than control group although no significant differences in mean values of blood glucose were observed . In this study it was found that endogenous insulin play an important role in the modulation of pain in cancer pain and also circadian rhythm influences cancer pain

INTRODUCTION

2. INTRODUCTION

Pain is an unpleasant sensation of hurt which signals current or impending tissue damage or a pattern of responses which operate to protect the organism from harm[1]. It is a complex experience and is highly subjective[2]. There are both acute and chronic painful conditions.

Cancer known medically as a malignant neoplasm, is a large group of different diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to other distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous. Benign tumors do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body[3].

Pain in cancer values priority because of many perspectives. In cancer patients, pain can affect the patient's quality of life and may in turn affect the patient's will to live or to cooperate in treatment. Pain is the first sign of malignancy and prevalent symptom experienced by cancer patients[6]. Pain further worsens already debilitated cancer patients condition[7] .

An estimated 6.6 million people from around the world die from cancer each year[10]. In the early diagnosis of disease, 30-50% of cancer patients experience pain while 70- 90 % of advance state cancer patients experience pain. When diagnosed 60-80% of patients, are diagnosed as advanced cases[11]. In cancer, pain can occur at any point during the course of the illness. Cancer pain depends on the type and stage of disease. Also pain in cancer can be due to the pain caused by cancer itself, by cancer treatment such as surgery, radiation, or chemotherapy, or by the side effects of treatment.

Pain management in cancer pain includes analgesics, surgery, nerve blocks, anticancer therapies and psychological techniques[12]. But often cancer pain remains prevalent and undertreated[14].

However pain remains a serious medical issue and pain control or pain relief remains a insignificant health care matter[15].

Various chemical mediators such as prostaglandins, bradykinin, 5-Hydroxytryptamine(5-HT), opioid and nonopioid peptides, enkephalins, β-endorphin and substance P, neurokinin-A, neurokinin-B, neurotensin, and cytokines are involved in pain [16]. 5-HT, bradykinins, opioid peptides, Ach, GABA(Gamma amino butyric acid) are chemical agents involved in the activation of nociceptors[2].

Insulin is a hormone regulating carbohydrate and fat metabolism in the body. It has been postulated in many studies that insulin has got antinociceptive action. The influence of morphine and ibuprofen on endogenous insulin in patients with cancer pain showed insulin's antinociceptive activity by a significant increase in serum insulin values[17].

Antinociceptive response was potentiated in mice due to the administration of insulin exogenously. The analgesic effect of insulin was mediated by 5-hydroxtryptamine, dopamine, NMDA (N-methyl-D-aspartate), opioidergic receptors and potassium and calcium channels[18]. Insulin showed antinociceptive activity without any hypoglycemic action when administered intra cerebroventricularly.Insulin modulated chronic pain rather than acute pain through some central mechanism mediated by dopamine,5-hydroxytryptamine and opioids.Release of endogenous opioids contribute to insulin's antinociceptive action[19]. Insulin increased the analgesic action of sodium salicylates[20].

Insulin is implicated in the modulation of pain threshold. Formalin induced pain was attenuated by insulin[19]. Another preclinical study revealed that antinociception was potentiated with flavones in mice, endogenous insulin level was significantly increased. This study also stated that there exists no relationship between glycemic state in acute painful condition and antinociceptive response. Insulin is involved in the modulation of pain in animals[21]. Exogenous administration of insulin induced hypoglycemia which ultimately raised the antinociceptive action of morphine in rats by the tail flick test[22]. Insulin may also function as a neuro modulator[18].

Circadian rhythm is the best known and probably most general rhythm in living creatures. It plays a very important role in the pattern of pain produced by various diseases. The pattern of pain observed in each clinical state is specific[2]. Cancer pain shows peak at 6pm and trough hours at 4-10 am[15] .Many studies reports time dependent variation in the perception of pain, its neurochemistry, and on drug treatment. Circadian variation in pain intensity could be the best marker to use in determining when analgesics should be administered. Pain treatment still remains inadequate because not enough attention has been given to time-of-day patterns of pain intensity[2] .Various mediators and hormones are released based on circadian rhythm. Insulin is a hormone and release of insulin in the body is based up on the circadian rhythm[23].

The above literatures signals that that hormone levels are influenced and released based on circadian rhythm. From further literatures it is clearly understood that there exists a relationship between insulin in painful condition, but insulin's role and mechanism in the modulation of pain is not clearly understood. However, this study was directed towards identifying the role of circadian rhythm on serum insulin level and blood glucose level and insulin's role in the modulation of pain.

REVIEW OF LITERATURE

3. REVIEW OF LITERATURE

3.1 PAIN:

One of the commonest symptom for which a person approaches medical care is pain. The International Association for the Study of Pain defines pain as "An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage"[1].

The American Academy of Pain Medicine defines pain as – "An unpleasant sensation and emotional response to that sensation"[1].

The Web version of the Encyclopedia Britannica defines pain as – "A complex experience consisting of a physiological (bodily) response to a noxious stimulus followed by an affective (emotional) response to that event. Pain is a warning mechanism that helps to protect an organism by influencing it to withdraw from harmful stimuli. It is primarily associated with injury or the threat of injury, to bodily tissues" [1].

Pain is a very complex phenomenon, characterized as an unpleasant sensation that diminishes person's normal patterns of patient's activity, sleep, appetite and thoughts. It is highly subjective, and factors such as anxiety, fatigue, suggestion, or emotion, as well as prior experiences can influence its perception[2].

3.2 TYPES OF PAIN:

Pain is of two types, acute and chronic.

ACUTE PAIN:

Acute pain is generally a signal of rapid-onset injury to the body, and it resolves when pain relief is given and/or the injury is treated. The cause is well defined. It may be due to illness, trauma, surgery or any painful medical procedures. Acute pain can sometimes be beneficial to patient in diagnosing a disease and treating it. The primary goal of acute pain treatment is to diagnose the source and remove it[1].

CHRONIC PAIN:

Pain is considered chronic when it lasts beyond the normal time expected for an injury to heal or an illness to resolve. Chronic pain, sometimes called persistent pain, can be very stressful for both the body and the soul. Chronic pain is pain that has outlived its usefulness and is no longer beneficial to the patient. The main goals of chronic pain treatment are to minimize the pain, limit disability and to improve person's functioning. Complete relief of pain is rare in chronic pain. The more realistic goal is to decrease the level of pain to a tolerable level that allows the person to focus on everyday activities[1]**.**

3.3 CANCER:

Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells. It is one of the major causes of death in the developed nations: The terms cancer, malignant neoplasm (neoplasm simply means 'new growth') and malignant tumor are synonymous. Both benign and malignant tumors manifest uncontrolled proliferation, but the latter are distinguished by their capacity for dedifferentiation, their invasiveness and their ability to metastasize[24].

3.4 CANCER PAIN:

Pain in cancer can be devastating. Pain in cancer is of great significance because it causes physical, psychosocial & psychological distress to the unfortunate victim, considerably damaging their personal and social lives[25].

3.5 TYPES OF CANCER PAIN:

Temporal categories of cancer pain include:

ACUTE PAIN:

- Related to a specific event (surgery, injury).
- Short lasting, as recover from the surgery, the pain at the incision goes away.
- Need for taking pain medicine is short. Pain disappears by taking strong medicine (a narcotic) to less strong medicine to no need for taking pain medicine

CHRONIC PAIN:

- Can last months to years even if cause of pain has healed (surgery) or been removed (chemo done).
- If untreated, pain signals continue and becomes remembered (feelings of pain continue) in your brain even after the pain is gone.
- This is real pain and is not just in mind.
- Affects sense of well-being and quality of life.
- Requires the use of pain medicine(s) for longer periods of time, possibly the rest of your life.

PHANTOM (LIMB) PAIN:

- Feeling that the limb or breast is still there even after it has been removed.
- Pain that may ache, throb or otherwise give an unpleasant or hurting feeling.
- The pain is real.

BREAKTHROUGH PAIN:

- Unexpected pain that occurs between doses of pain medicine (called a pain flare).
- Pain gets very bad in 3-5 minutes.
- Pain flares may last about 30 minutes.
- Each time pain flares are not same.
- Usually treated with a pain medicine that acts very quickly and doesn't last for long.

- Usually means pain medicine needs to be adjusted (may need more medicine)

PAIN FLARES can be caused by:

- Doing something like moving, gardening.
- Pain medicine does not last as long or relieves pain as it should.
- Sometimes there is no obvious cause; the pain flare just happens.

Physiologic categories of cancer pain include:

NEUROPATHIC PAIN (INVOLVES NERVE ENDINGS): NERVE DAMAGE BY TUMOR OR CANCER TREATMENT:

- The nerve is injured or squeezed by the cancer or cancer treatment.
- Pain may be felt as burning, shooting, stabbing, or numbness. Some say it feels like pins and needles.
- Sometimes called peripheral neuropathy

NOCICEPTIVE PAIN:

- Pain arising from damage to tissues other than nerve fibers. It is also called **tissue pain**. The undamaged nerve cells called nociceptors carry the sensation to spinal cord from where it is relayed to the brain. It is called somatic pain if it results from injury to muscles, tendons and ligaments.
- Somatic pain is usually well localized. It is called visceral pain if it results from injury to the internal organs like stomach, gall bladder and urinary bladder. Visceral pain is usually diffuse and non-localizing.
- Somatic pain in turn is classified in to cutaneous somatic pain if the pain arises from the skin and deep somatic pain if it is from deeper musculoskeletal tissues. The various causes of joint pain are grouped under musculoskeletal pain.

3.6 EPIDEMIOLOGY:

An estimated 6.6 million people from around the world die from cancer each year[10]. In the early diagnosis of disease, 30-50% of cancer patients experience pain while 70- 90 % of advance state cancer patients experience pain. When diagnosed 60-80% of patients, are diagnosed as advanced cases[11].

Cancer prevalence in India is estimated to be around 2.5 million, with over 8, 00,000 new cases and 5, 50,000 deaths occurring each year.

3.7 AETIOLOGY OF CANCER PAIN:

Not everyone who has cancer has pain. For those who do have pain, there are many different causes:

CANCER ITSELF:

The cancer itself causes about 65%-80% of cancer pain

- Pressure of the tumor on an organ (liver, lungs), bone or nerves
- Cancer growth into bone, nerves or an organ
- Sometimes cancer can cause pain when blood vessels become obstructed by the tumor.

CANCER TREATMENTS:

The cancer treatments cause about 15%-25% of pain

- Chemotherapy
    - Mouth sores
    - Numb fingers, feet
    - Bone or joint pain
- Surgery
    - Cutting across a nerve during surgery
    - Pain from incision
- Radiation therapy

- Nerve ending sensitivity
- Skin irritation
- Procedures for treatment, evaluation or diagnosis (cause about 5%-10% of pain)

- Biopsy (cutting out the cancer or a a piece of the cancer to make a diagnosis)
- Blood draws (using a needle to remove blood from a vein)
- Placing a needle into the spine area (back bone) to give medication (called a lumbar puncture) also could be used to give pain medication
- lumbar punctures, laser treatments, bone marrow tests etc. can cause pain
- Not related to cancer or cancer treatment
    - Other diseases (diabetes, heart problems, arthritis)
    - Injury (car accidents)

THE DIFFERENT CAUSES FOR PAIN IN PEOPLE WITH CANCER:

- Physical from the cancer or the treatment
- Intellectual - knowledge, memory loss, self-control, review of life issues
    - Emotional pain anxiety, fear, grief
    - Interpersonal pain burden, physical needs, overprotection
    - Financial pain costs, loss of job
    - Spiritual pain facing death, questions of faith, feelings
    - Bureaucratic pain - more doctors, tests, questions[25]

3.8 PATHOPHYSIOLOGY:

Pain is initiated by stimulation of nociceptors in the peripheral nervous system, or by damage to or malfunction of the peripheral or central nervous systems .A nociceptor is a sensory receptor that reacts to potentially damaging stimuli by sending nerve signals to the spinal cord and brain. This process, called nociception, usually causes the perception of pain. In mammals, nociceptors are sensory neurons that are found in any area of the body that can sense pain either externally or internally. Nociceptors neuron sensitivity is modulated by a large variety of mediators in the

extracellular space. Peripheral sensitization represents a form of functional plasticity of the nociceptors.

BASIC PROCESS OF NOCICEPTIVE PAIN TRANSMISSION:

STIMULATION-Noxious stimulus sensitizes and/or stimulates nociceptors and causes the release of neural chemicals that also sensitize and/or stimulate nociceptors. This activation leads to the production of an action potential.

TRANSMISSION- The action potential continues from the site of noxious stimulus to the dorsal horn of the spinal cord and then ascends to higher centres in the CNS. Transmission takes place in atleast five pathways:

a.Spinothalamic tract

b.Sspinoreticular tract

c.Spinomesencephalic tract

d.Dorsal column postsynaptic spinomedullary pathway

e.Propriospinal multisynaptic ascending systems

PERCERPTION-Conscious experience of pain

MODULATION-Inhibition of nociceptive impulses. Neurons from the brain stem descend to the spinal cord and release substances such as endogenous opioids, serotonin, and nor epinephrine that inhibit transmission of nociceptive impulses[27].

Fig 1. Schematic representation of Pain Pathway.

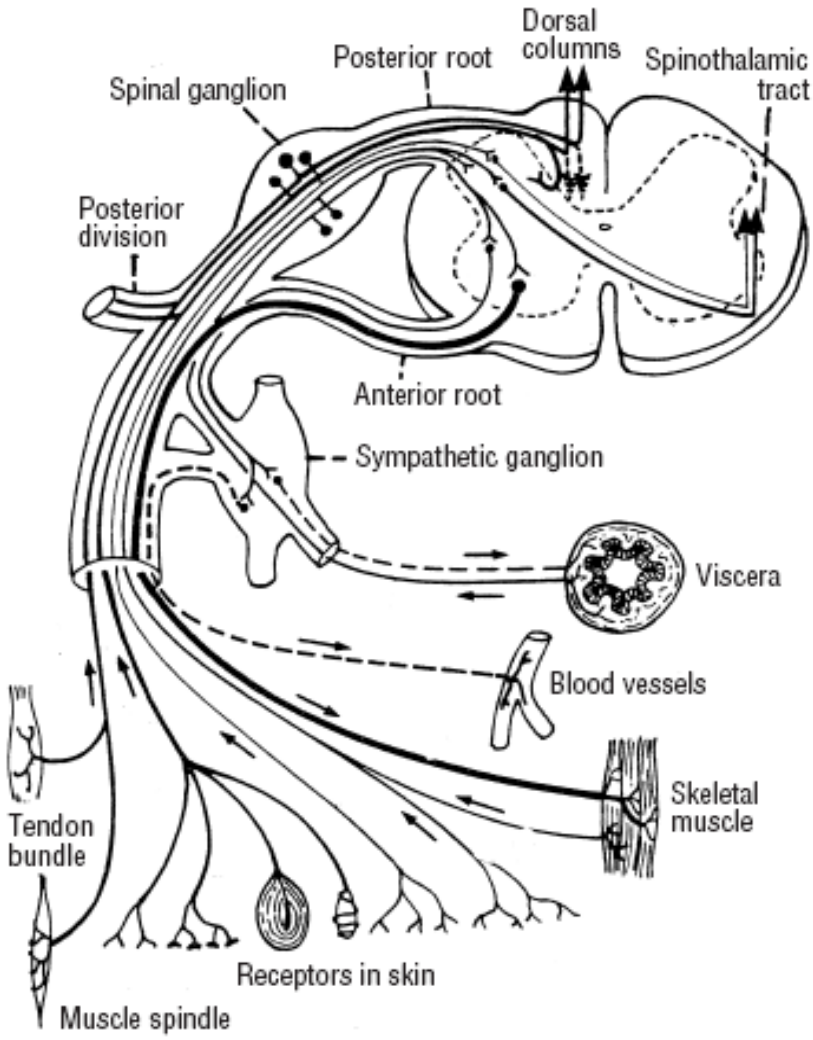
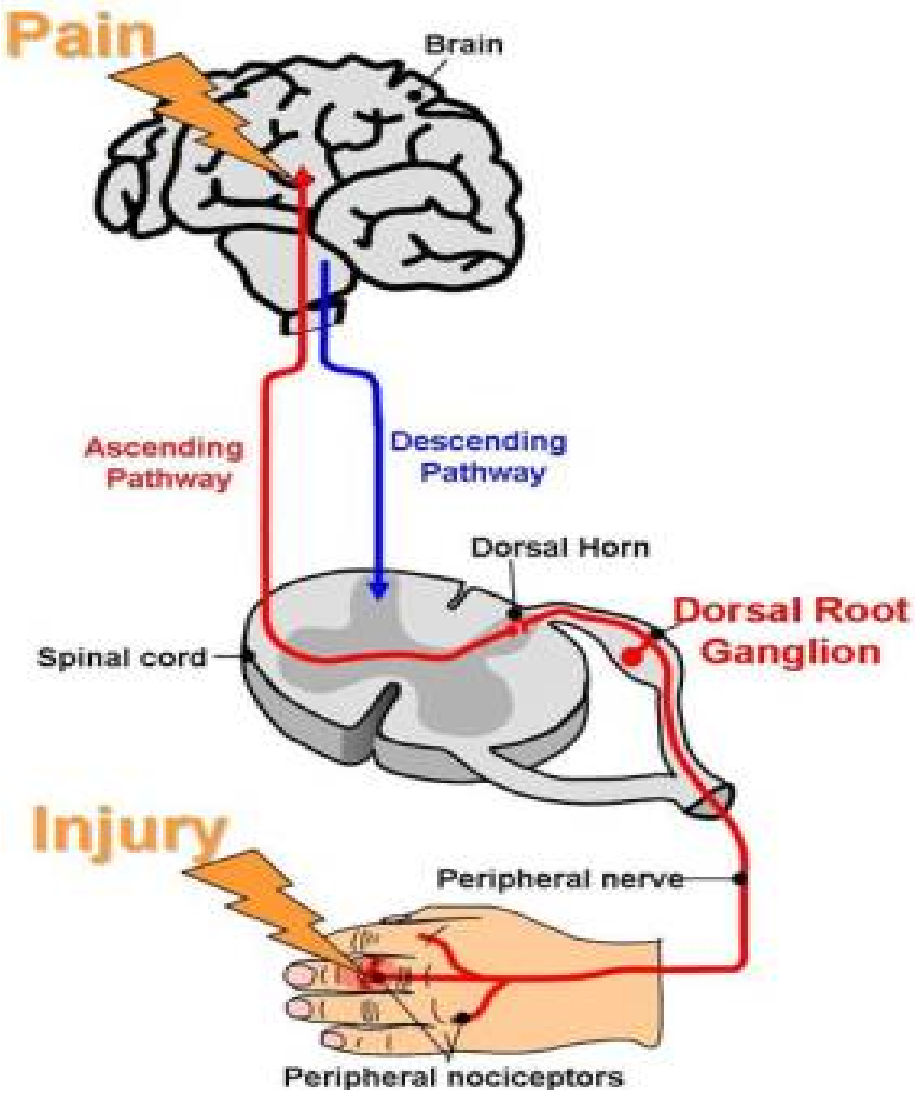


Fig.2 Ascending and Descending Pain Pathway.



3.9 SIGNS AND SYMPTOMS OF CANCER PAIN:

- Acute pain
- Chronic pain
- Superficial pain
- Visceral pain is usually diffuse and non-localizing.

- Somatic pain is usually, dull, aching, usually well localized pain. Somatic pain in turn is classified in to cutaneous somatic pain if the pain arises from the skin and deep somatic pain if it is from deeper musculoskeletal tissues. The various causes of joint pain are grouped under musculoskeletal pain.
- Neuropathic pain is the pain caused by lesion in the nervous system when they are structurally or functionally damaged. It is called central pain if the lesion is the central nervous system. It is called peripheral neuropathic pain if the lesion is in the peripheral nervous system. The neuropathic pain is described as severe, sharp, lancinating, lightning-like, stabbing, burning, cold, numbness, tingling or weakness. It may be felt traveling along the nerve path from the spine down to the arms/hands or legs/feet[25].

3.10 DIAGNOSIS OF CANCER PAIN USING PAIN ASSESMENT SCALES:

The most commonly used scales are visual analogue and verbal rating scale. Visual analogue scales are lines 10 cm long with the extremes at each end labeled usually “no pain at all” and “worst pain imaginable” respectively. The patient is required to mark the severity of the pain between the two extremes of the scale. Verbal rating scales use adjectival descriptors such as ‘none’, ‘mild’, moderate and excruciating. More elaborate questionnaires such as the McGill pain questionnaire helps to describe other aspects of the pain and pain diaries record the influence of activity and medication on pain[26].

3.11 CANCER PAIN MANAGEMENT:

Cancer pain management aims at ensuring the quality of life in cancer patients. Pain in cancer has been conceptualized as a multidimensional phenomenon, which needs multidisciplinary care. In cancer pain, drug treatment is the mainstay of pain management. Between 70% and 90% of all cancer pain can be controlled with oral medication. Adequate pain relief can be achieved in more than 75% of patients who receive optimal analgesic management using simple techniques such as opioids, non-opioid analgesics, and adjuvant medications, as suggested by the World Health Organization's analgesic ladder. It is recommended that drugs should be given by mouth, by the clock, tailored to the individual patient. However pain relief remains inadequate in cancer pain patients.

- Non opioid analgesics
- Opioid analgesics
- Adjuvant drugs
- WHO three step analgesic ladder
- Advanced pharmacological strategies
- Interventional strategies
- Psychological therapies
- Supportive therapies
- Physical therapies
- Anticancer therapies

Acetaminophen (paracetamol) or **nonsteroidal anti-inflammatory drugs (NSAIDs)** are effective analgesics for patients with mild cancer pain and can be combined with opioids in patients with moderate to severe pain. Experience with the use of WHO ladder has shown that the simple principle of escalating from non-opioid to strong opioid analgesics is safe and

effective. Nonopioid analgesics prevent formation of prostaglandins produced in response to noxious stimuli, thereby decreasing the number of pain impulses received by the CNS.

OPIOIDS are very effective for the relief of moderate to severe pain. Many patients with cancer pain, however, become tolerant to opioids during long-term therapy. Therefore, increasing doses may be needed to continue to relieve pain. A patient's tolerance of an opioid or physical dependence on it is not the same as addiction (psychological dependence). Mistaken concerns about addiction can result in under treating pain.

TYPES OF OPIOIDS :

There are several types of opioids. Morphine is the most commonly used opioid in cancer pain management. Other commonly used opioids include hydromorphone, oxycodone, oxymorphone, methadone, fentanyl, meperidine (Demerol), tapentadol, and tramadol.

In most patients, side effects associated with the use of opioids can be easily managed with a combination of patient education and reassurance about the transient nature of sedation and emesis, careful selection of dose and route of opioid, and the use of additional drugs such as antiemetics and laxatives.

SIDE EFFECTS OF OPIOIDS:

Nausea,constipation,vomitting

ADJUVANT DRUGS are used for difficult pain syndromes including neuropathic and bone pain. Among the agents frequently used for the management of neuropathic pain, tricyclic antidepressants, systemic local anesthetics, and baclofen have been traditionally used for dysesthetic pain, whereas anticonvulsants such as gabapentin, carbamazepine, and phenytoin have been more frequently used for the management of lancinating pain[28].

Incidental pain, defined as pain that is sudden and severely aggravated as a result of movement, swallowing, defecation, or urination, is usually controlled if the patient remains immobile or refrains from performing the painful maneuver. Other techniques to increase local control of incidental pain episodes include radiation therapy, orthopedic procedures, or neurological

procedures such as percutaneous cordotomy. **Bisphosphonates** are useful in relieving both the continuous and the incidental pain components in patients with bone cancer pain[29].

Pain can also be relieved by modification of the disease process when appropriate with surgery, chemotherapy, and radiotherapy. Other methods include psychological interventions, physical therapy, and complementary medicine.

About 10% of patients may require **interventional techniques** (peripheral nerve blocks, autonomic nervous system blocks,radiofrequency lesions, and neurosurgical procedures) for some pain problems as part of a multimodal, multidisciplinary approach to pain control.

For pain not controlled with oral medications, low doses of an opioid plus a local anesthetic can be delivered by the spinalor epidural routes to provide relief with relatively few side effects. Systems used for chronic intraspinal opioidadministration include percutaneous tunneled epidural or spinal catheters, tunneled catheters connected to subcutaneously implanted injection ports, and implanted infusion pump systems [30].

3.12 INSULIN:

Insulin is a two chain polypeptide hormone having 51 amino acids and MW about 6000.It is synthesized by beta cells in the islets of Langerhans . It is made up of two chains, an A chain containing 21 amino acids and a B chain containing 30 amino acids, linked by two cysteine disulphide bridges. The gene for insulin is on the short arm of human chromosome 11[31,32].

3.13 FUNCTIONS OF INSULIN:

Insulin is a hormone that is central to regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscles. Insulin is synthesized in significant quantities only in beta cells in the pancreas. When the beta cell is appropriately stimulated, insulin is secreted from the cell by exocytosis and diffuse into islet capillary blood. Insulin is secreted in primarily in

response to elevated blood concentrations of glucose. Some neural stimuli and increased blood concentrations of other fuel molecules, including amino acids and fatty acids also promote insulin secretion[33].

IMPORTANT FUNCTION OF INSULIN:

Elevated concentrations of glucose in blood stimulate release of insulin, and insulin acts on cells throughout the body to stimulate uptake, utilization and storage of glucose. The effects of insulin on glucose metabolism vary depending on the target tissue. Two important effects are:

- Insulin facilitates entry of glucose into muscle, adipose and several other tissues.
- Insulin stimulates the liver to store glucose in the form of glycogen.

In addition to its role of regulating glucose metabolism, insulin also

- Stimulates lipogenesis
- Diminishes lipolysis
- Increases amino acid transport into cells
- Modulates transcription
- Altering the cell content of numerous mRNAs
- Stimulates growth
- DNA synthesis
- Cell replication [35]

3.14 FATE OF INSULIN:

Insulin is distributed only extracellularly.It is a peptide gets degraded if given orally. The average daily secretion is about 2 mg (50 units).The half life of insulin is about 4 minutes. It is metabolized chiefly (about 80%) in liver and to a smaller extent in kidneys. About half is inactivated during first pass in the liver by insulin glutathione transhydrogenase which cleaves the molecule into A and B chains. The rest are inactivated in the kidney and other tissues by insulinases.[31,32]

Insulin is metabolized in the liver, kidney, and muscle. Glucose stimulates insulin secretion through a series of regulatory steps that begin with its transport into the beta cells by the GLUT 2 transporter. Further metabolism of glucose via glucose- 6- phosphate and pyruvate generates ATP which inhibits the activity of ATP sensitive potassium channels. The inhibition of this potassium channel induces opening of voltage-dependent calcium channels and stimulation of insulin secretion[36].

Insulin promotes glucose entry across cell membrane into the cells of heart, muscle, adipose tissue and all other tissues except brain, liver, renal tubules, intestinal mucosa, islet cells and RBCs. Insulin Increases peripheral utilization of glucose, increases glycogenesis, decreases gluconeogenesis and favours conversion of glucose to fat. Insulin promotes protein anabolism and inhibits protein catabolism in liver, muscle and other cells. It also has a protein sparing action. Insulin promotes lipogenesis, inhibits lipolysis. Insulin promotes potassium and phosphate entry into cell. Insulin reduces sodium uptake [32].

3.15 INSULIN RECEPTORS:

Insulin receptors are present in all cell membranes but their density depend on the cell type, for example liver and fat cells are very rich. Insulin receptors are heterotetrameric glycoprotein's consisting of two extracellular alpha and two transmembrane beta sub units linked together by disulfide bonds. It is oriented across the cell membrane as a heterodimer.The alpha subunits carry insulin binding sites while the beta subunits have tyrosine protein kinase activity. Insulin acts on specific receptors located on the cell membrane of a cell. Excess insulin decreases and low insulin increases the number of insulin receptors.[31,32].

It has been postulated in many studies over the years that insulin is involved in the modulation of pain. However clinical studies regarding this is very scarce.

3.16 CLINICAL STUDY ON PAIN:

A clinical study reported on the influence of morphine and ibuprofen on endogenous insulin and various biochemical parameters in patients with cancer pain. The results of the study showed serum insulin values in cancer patients showed significant increase although no significant differences in blood glucose, HDL, albumin and total protein level[17] .

In a study it was reported high insulin level in patients with pain in the neck, shoulder and back. The study revealed physiological and psychological have been proposed to link stress and musculoskeletal pain. The study showed changes in P-endothelium , S-insulin, P-fibrinogen, S-testosterone, S-albumin, and S-growth hormone[37].

Another clinical study in prader will syndrome patients (PWS) revealed, thermal and pain thresholds were significantly higher than in healthy and obese people. Most of the sensory thresholds were altered in PWS people. Serum insulin levels were significantly increased and QUICKI (quantitative insulin sensitivity check index) decreased[38].

A study was done to show a possible relationship between pain and insulin level in various painful conditions like trauma, arthritis, toothache, cancer pain. The magnitude of this relationship was observed more in cancer pain (unpublished data.)

A study reports in humans, Insulin stimulates synthesis of the vasoconstrictor peptide endothelin-1 (ET-1) by cultured vascular endothelial cells[39].

A study revealed acute severe pain decreases insulin sensitivity, primarily by affecting nonoxidative glucose metabolism in humans. Ten healthy male volunteers underwent two randomly sequenced hyperinsulinemic-euglycemic clamp studies 4 weeks apart. Self-controlled painful electrical stimulation was applied to the abdominal skin for 30 min, , to a pain intensity of 8 on a visual analog scale of 0-10, just before the clamp procedure. The study reported a twofold to threefold increase in concentrations of epinephrine, cortisol, growth hormone, glucagon and free fatty acids during pain[40].

In a study it was reported that in In vitro, insulin-like growth factor-I (IGF-I) has been shown to prevent neuronal apoptosis, to increase axonal growth, and to support myelination. But by using a double-blind, placebo-controlled design, 40 patients were randomized to treatment with

recombinant human IGF-I or placebo for 6 months. There were no significant adverse events and minor adverse events occurred equally in both groups. IGF-I was safe, but did not improve symptoms in this 6-month trial[41.]

Another study analyzed blood plasma biochemical parameters in patients with pain of vascular origin. The biochemical parameters such a s C reactive protein, total protein, albumin, total cholesterol, HDL and LDL cholesterol, glucose, triglycerides, reduced glutathione, malondialdehyde (MDA), and total antioxidative capacity changed in relation to pain intensity. This study also stated that at different time intervals, pain intensity was related to different biochemical markers. This study finally concluded blood plasma changes might play an important role in pain assessment and pain management[42].

Another study was done to investigate biochemical parameters in the blood serum can establish and discriminate pain intensity of different etiology. The patients with acute pancreatitis, patients with bone fractures and patients without pain were included in this study. Whole serum proteins, albumin, C-reactive protein, glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglyceroles (triglycerides), apolipoprotein-B and electrophoretic levels of alpha-lipoprotein, beta-lipoprotein and pre-beta-lipoprotein were analyzed. The results of this study revealed in both diagnoses during persisting pain, the products of lipid metabolism such as triacylglyceroles and HDL-cholesterol were enhanced together with glucose levels. Electrophoretic measurements, revealed higher levels of beta-lipoproteins in fractures, and increased values of pre-beta-lipoproteins and alpha-lipoproteins in both groups of patients suffering from pain. This study also stated acute stress generally influences glucose levels so that their increase cannot be considered as a specific marker of pain intensity[43].

3.17 PRECLINICAL STUDY ON PAIN:

The present study investigates the possible mechanisms of insulin antinociception in mice using the tail flick test. Mice were treated with insulin and the antinociceptive effect of modulators of 5-HT, NMDA, dopamine, opioids, potassium and calcium channels was tested, followed by blood sugar estimation. All drugs were given 30 min prior to insulin administration. Pretreatment with morphine (opioid agonist), 5-Hydroxytryptophan (5-HTP; 5-HT precursor), nicorandil (K(+) channel opener) and nimodipine (Ca(+) channel antagonist) significantly ($p < 0.001$) potentiated insulin antinociception, whereas naloxone (opioid antagonist), ketanserin (5-HT(2) receptor antagonist), pCPA (5-HT depleter), ondansetron (5-HT(3) receptor antagonist), L-dopa (dopamine precursor), reserpine (dopamine depleter), ketamine (NMDA receptor antagonist) and glibenclamide (K(+) channel blocker) significantly antagonized insulin antinociception ($p < 0.001$). Results suggest that 5-HT, dopamine, NMDA, opioidergic receptors and potassium and calcium channels play a significant role in insulin analgesia[18].

A study reported both glucose and insulin pretreatment in rats in certain doses were found to potentiate and prolong significantly the analgesic action of morphine[22].

The analgesic effect of sodium salicylate was doubled by the administration of insulin. The analgesic action of sodium salicylate was estimated by its prolongation of reaction time to a thermal stimulus and its level in tissue was determined chemically. Animals receiving insulin were given sufficient glucose to prevent hypoglycemia. Insulin injection doubled the analgesic effect of sodium salicylate and doubled its concentration in brain, heart and skeletal muscle. In alloxan-diabetic mice, both the action of S and its level in these tissues were decreased and were corrected by the administration of insulin. These results show that the transport of S across certain cell membranes is insulin-dependent[20.]

Insulin attenuates chronic rather than acute pains through a mechanism mediated by dopamine, 5-hydroxytryptamine and opioids without any hypoglycemic action. This study reveals that insulin induced antinociception may be due to some central mechanism. Intracerebroventricular doses of insulin dose-dependently reduced formalin-induced nociceptive responses[19].

Endogenous insulin level was significantly increased when antinociception was potentiated in mice. Flavanoid group of substances has been shown to elicit opioid mediators' antinociceptive

response in experimental tools.[44-46].This study reveals statistically insignificant glucose level changes. The hypo- and hyperglycemic conditions were induced physiologically through swim stress and external dextrose administration respectively in mice. The anti-nociception was assessed by acetic acid assay, blood glucose measured using glucometer and serum insulin by radioimmunoassay. A reduction in blood glucose level and elevation in serum insulin level when compared with flavones treatment was observed[21].

Insulin receptors are widely but unevenly distributed in the brain. Insulin has been reported to be involved in the regulation of neurotransmitters release. The results of this study showed that insulin has no analgesic activity; however, it caused significant central inhibitory effects by decreasing both locomotor activity and also decreased the exploratory behavior. The study concluded insulin has several neuropharmacological effects[47].

A study aimed to find out the antinociceptive effect of insulin and its combinations with resveratrol and curcumin in attenuating diabetic neuropathic pain. The study also examined the effect of these combinations on tumor necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) levels in streptozotocin (STZ) induced diabetic mice. Four weeks after a single intraperitoneal injection of streptozotocin , mice were tested in the tail immersion and hot-plate assays. Diabetic mice exhibited significant hyperalgesia along with increased plasma glucose and decreased body weights compared with control mice. Chronic treatment with insulin and its combinations with antioxidants significantly attenuated thermal hyperalgesia and the hot-plate latencies. There was a significant inhibition of TNF-alpha and NO levels . These results indicate an antinociceptive activity of resveratrol and curcumin and point towards the beneficial effect of these combinations with insulin in attenuating diabetic neuropathic pain, possibly through the participation of NO and TNF-alpha[48].

A study reported systemic administration of clonidine and yohimbine respectively produced dose-dependent analgesic and hyperalgesic effects in control animals. Both of these phenomena were impaired in chronically diabetic animals. But insulin-treated diabetics displayed supersensitivity to clonidine's antinociceptive effect, especially at low doses[49].

Diclofenac, dipyrone, ketorolac, lysine acetyl salicylate, and sodium salicylate were injected intradermally into mice tails and evaluated the tail-flick response to radiant heat. These results were compared with intraperitoneally injected controls. This study also evaluated the ability of naloxone to reverse the observed effects. The results of the study suggested local, but not systemic, administration of NSAIDs produced antinociception in the tail-flick thermal assay. The endogenous opioid system contributes to the peripheral anti-nociceptive effects of dipyrone, but not to that of diclofenac, ketorolac, lysine acetyl salicylate, or sodium salicylate, suggesting differences in the mechanisms of action among the NSAIDs[50].

A preclinical study stated one of early signs of diabetic neuropathy in STZ-treated rats, mechanical hyperalgesia, can be triggered by moderate insulinopenia, irrespective of glycemic status of the animals. This study evaluated the role of insulinopenia in nociceptive abnormalities in the streptozotocin (STZ) rat model of diabetes to test the hypothesis that, in addition to hyperglycemia, impairment of insulin signaling may be involved in progression of neuropathy.. The pain thresholds observed did not correlate with blood or nerve glucose or sorbitol levels, but both correlated with plasma insulin level in STZ-normoglycemic rats, and low-dose insulin replacement normalized the pressure threshold without affecting blood glucose level[51].

Enkephalins may have a neurotransmitter role in both brain and peripheral tissues and that methionine- and leucine-enkephalin haves eparate neuronal functions. The highest proportions of leucine-enkephalin were found in the cerebral cortex and hippocampus.In painful condition endogenous,opioid peptides play an important role in pain perception[52].

A study reported that some factor(s) derived from spleen mononuclear cells is the prime factor involving the insulin-insensitive mechanisms for the reduction of mu-opioid agonist-induced antinociception during the severe stages of diabetes[53].

Clonidine induced antinociception is independent of its hyperglycemic action. In contrast to morphine, clonidine induced antinociception seems not to involve ATP sensitive potassium channels; rather its antinociception is enhanced by the blockade of these channels. This enhancement is attributed partially to an adrenergic mechanism excluding the opioid pathways.

The results favour the contention that the mechanisms K involved in the antinociception induced by clonidine and morphine are different[54] .

Another study reports that 7-hydroxy flavone induces antinociception like morphine, utilize ATP sensitive potassium channel at the cellular level .The results of this study reveals no cause-effect relationship between the changes in the glycaemic and algesic state. But insulin which is controlled by ATP sensitive potassium channel at the cellular level modulates antinociception exhibiting a cause-effect relationship between them[55.]

The effects of pretreatment with protein kinase C and protein kinase A inhibitors on the intraventricular insulin-induced attenuation of the antinociceptive effect of [D-Ala2, N-MePhe4, Gly-ol5]enkephalin (DAMGO) were studied in mice. Intracerebroventricular (i.c.v.) pretreatment with insulin dose- and time-dependently attenuated the antinociceptive effect of i.c.v. DAMGO in mice. These results suggest that the reduction of DAMGO-induced antinociception by insulin in mice may be, in part, due to the activation of protein kinase C followed by the activation of tyrosine kinase[56].

Another study reported effects of intravenous sodium salicylate administration on plasma concentrations of insulin, free fatty acids (FFA) and glucose in intact, anaesthetized dogs both during basal and isoprenaline stimulated lipolysis. In both situations sodium salicylate reduced the plasma concentrations of insulin. The reduction was associated with decreased plasma FFA concentrations and FFA turnover rate, while plasma glucose concentrations remained unaltered. The reduced plasma insulin concentrations effected by sodium salicylate is most likely secondary to the concomitant fall in plasma FFA concentrations due to inhibition of FFA mobilization from adipose tissue[57].

3.18 CIRCADIAN RHYTHM:

Cells are the fundamentals of life. All life's processes happen in and by cells. One of the most amazing characteristics of cells is the fact that they sense what time it is. *We* humans possess a 'biological clock' . During the night our body works differently from the daytime. We have a lot

of different clocks in our body, possibly even one in every cell. Homeostasis is a system that makes the organism - up to a certain level - independent of its environment. Homeostasis is the possibility every living system has to keep its inner system balanced, like our body keeps its temperature constant, independently of the outside temperature. Many processes happen adapted to day or night, or to the seasons. Often organisms are so adapted to day and night that they have a system that causes the adaptation already before night falls or morning begins. Biological clocks take care that things happen at the right time. Homeostasis is nowadays seen as one of the fundamental aspects of life, having a biological clock may be as fundamental. The best way for an organism to keep its homeostasis is to prepare itself in time before a change occurs.

DEFINITIONS:

CHRONOBIOLOGY: Derived from chronos (time), bios (life), and logos (study of) is the objective description of biological time structures and plays an important role in medicine**.**

CHRONOPHARMACOLOGY: is the science concerned with the variations in the pharmacological actions of various drugs over a biological timings and endogenous periodicities.

Chronobiology, studies the biological rhythms:

CIRCADIAN RHYTHM: is defined as oscillations in the biological, physiological and behavioral function of an organism with a periodicity of 24 hrs. lasts about one day, like the sleep-waking rhythm, the body temperature, but also our sensitivity to pain or alcohol, reaction time, levels of hormones in the blood etc. Many patterns of change in plants and animals happen every day, always after about 24 hours. This circadian rhythm is the best known and probably most general rhythm in living creatures.

Biological clock is a miniscule piece of the brain (20 000 cells in all) just above the chiasma opticum (the place where the optic nerves are crossing). The suprachiasmatic nucleus (SCN) is no bigger than a quarter of a cubic millimetre. Because it is so close to the optic nerve it can get information directly from the eyes. The SCN is the site of the central pacemaker capable of synchronizing the cellular rhythms to produce observable circadian rhythms in different physiologic measures[58,59].

Pain due to several pathological conditions exhibits temporal variations in intensity throughout the circadian cycle[61].

Circadian patterns of pain experience have been studied in various clinical disease states. For example, pain in rheumatoid arthritis occurs mostly at the beginning of the day[62] whereas pain due to osteoarthritis occurs mostly at the end of the day[63].The migraine headaches showed a circadian pattern with more attacks occurring in the morning hours (08:00–12:00) compared to midnight.[64] Also, the circadian pattern of dental pain were maximal in the early afternoon and minimal in the early morning.[65].This clearly indicates that circadian rhythm influence pattern of pain in various diseases.

3.19 CIRCADIAN RHYTHM OF PAIN:

The circadian (24-h) time structure showed great importance to the practice of medicine and pharmacotherapy of patients. . Rhythmicity in the pathophysiology of disease is one basis for chronotherapeutics. For effective treatment, purposeful variation in time of the concentration of medicines in synchrony with biological rhythm determinants of disease activity. Also a second basis to control the undesired effects of medications, especially when the therapeutic range is narrow and the potential for adverse effects high, which is the case for cancer drugs. A third basis is to meet the biological requirements for frequency-modulated drug delivery, which is the case for certain neuroendocrine peptide analogues[66].

Pain varies tremendously from patient to patient. Intensity of pain varies according to time of day. A circadian pattern of pain was found in patients suffering from pain produced by different diseases. For instance, highest toothache intensity occurred in the morning, while biliary colic, migraine, and intractable pain were highest at night. Patients with rheumatoid arthritis reported peak pain early in the morning, while those with osteoarthritis of the knee indicated that the maximal pain occurred at the end of the day. The effectiveness of opioids appears also to vary according to time of day, but large differences in the time of peak and low effects were found. . Investigators found that peak pain intensity and narcotic demands occurred early in the morning, while others found maximal pain at the end of theday[2].

The modulatory effects of sleep and circadian rhythmicity on glucose regulation appear to have important clinical implications for the diagnosis and treatment of abnormalities in carbohydrate metabolism[67].

A study reported dosing-time-dependent changes in the effect and toxicity of morphine were seen in mice keptunder 12h light and dark cycles. The magnitude of the analgesic effect of morphine depended on dosing time, with minimum effect at 02:00 h and maximum effect at 14:00 h. The serum hepatic enzyme levels of AST and ALT increased after dosing morphine at 02:00 and 14:00 h. However, hepatic glutathione, which is involved in the detoxification of chemical compounds, significantly decreased after i.p. morphine injection at 02:00 but not at 14:00 h. The results suggest that the analgesic effect of morphine is greater after dosing during the resting than during the activity phase of mice that have been induced with bradykinin-mediated pain. Drug-induced hepatic damage as inferred by GSH alteration, however, may be greater after dosing during the active phase[68].

The pharmacological effects and toxicity of KE-SI-TO (KST), analgesic and antipyretic drug, was investigated depending on the dosing time in mice. Circadian rhythms were demonstrated for analgesic and hypothermal effects of KST with higher values in the dark and lower ones in the light. Injection of KST resulted in a parallel increasing in latency to hot plate and a parallel decreasing in rectal temperature. KST induced toxicity was also observed depending on the dosing time[69].

The fish under dimecron (an organophosphate pesticide) toxicity was investigated by estimating the serum levels of T3 (triiodothyronine), T4 (thyroxine), cortisol, prolactin and insulin in control and sub-lethal dimecron-exposed fish for 1, 6, 12, 24h and 5 days. The fish exposed to sub-lethal concentration of dimecron showed varying changes in the levels of these serum hormones.The study showed reduced levels of thyroid hormone (T3) as well as the glucocorticoid hormone (cortisol) in the the fish which indicated they maintained a low metabolic rate, which is advantageous for the fish to indirectly reduce the toxic impact of the pesticide.Also elevated levels of prolactin were observed which indicated hydromineral regulatory effect of the hormone , and increased insulin level in the fish under pesticide stress is indicated its role in favoring an adaptive tissue glycogenesis besides a possible increased

lipogenesis to sequester the pesticide residue thereby reducing the toxic effect of the pesticide. The prolonged exposure of the fish (for 5 days) to sub-lethal dimecron appeared to exhibit a uniform recovery response in the different hormonal levels of the fish[70].

A study reported the time at which acetylsalicylic acid is administered is important in the actions of acetylsalicylic acid. The rhythmic patterns of acetylsalicylic acid induced analgesia and hypothermia resembled overall the rhythms occurring in the non-drugged state. Injection of acetylsalicylic acid resulted in a parallel increase in latency to hot plate and a parallel decrease in rectal temperature. Also a significant circadian rhythm in acetylsalicylic acid induced toxicity with the highest mortality at 17:00 and the lowest one at 05:00 . Dosing time dependent kinetics of salicylate seems to be related to the rhythm of toxicity of the drug[71] .

A study reported the hypothalamic–pituitary–adrenal axis (cortisol) and of the pineal gland (melatonin) altered functioning is responsible for the clinical circadian symptoms of RA.Human proinflammatory cytokine production exhibits a diurnal rhythmicity with peak levels during the night and early morning, at a time when plasma cortisol (anti-inflammatory) is lowest and melatonin (proinflammatory) is highest. Sex hormones also seem to be involved in circadian rhythms of RA symptoms. Increased pain intensity and sleep disturbances are observed during the luteal phase in patients who have RA, when estrogen (and progesterone) levels would be higher than in the follicular phase[72].

Another study revealed pain and pain intensity is circadian time dependent. Adequate pain relief is possible by taking this into account and thus developing new chronotherapeutic strategies and drug delivery systems.

The study confirmed circadian, circaseptan or circannual variations were seen in experimental inflammation and in patients with arthritis diseases. Morning stiffness observed in RA patients has become one of the diagnostic criteria of the disease. The data showed that signs and symptoms of rheumatoid arthritis (RA) vary between individuals, within a day and between days. The results of the study revealed circadian and circannual variations in the effectiveness, toxicity and pharmacokinetics of NSAID (non-steroidal anti-inflammatory drugs). A review of the available data suggests that peak and trough values found in different arthritic diseases do not

occur at the same hour of the day and that the side effects produced by NSAID are more important after the morning than the evening administration[73.]

The day/night pattern in leptin is caused by the combined effects of endogenous circadian pacemaker and day/night patterns in behaviors. The data imply that alterations in the sleep/wake schedule would lead to an increased daily range in circulating leptin, with lowest leptin upon awakening, which, by influencing food intake and energy balance, could be implicated in the increased prevalence of obesity in the shift work population[74.]

AIM AND OBJECTIVE

4. AIM & OBJECTIVE

- To estimate the amount of endogeneous insulin level and glucose level in cancer pain patients during day and night cycle

OBJECTIVE

- To determine the serum insulin level and glucose level in cancer pain patients taking opioid and Nonopioid analgesics and in cancer patients without pain during day and night cycle.
- To evaluate the role of endogenous insulin in pain threshold and to assess insulin's antinociceptive activity.
- To evaluate the role of circadian rhythm on endogenous insulin level during day and night cycle.
- To evaluate the role of circadian rhythm on glycemic level during day and night cycle.

PLAN OF WORK

5. PLAN OF WORK

- Identification of scope of work
- Literature survey
- Preparation of protocol for study
- Designing the Performa
- Obtaining approval from the ethical committee
- Obtaining consent from the hospital
- Data collection
- Analysis of the data
- Blood sample collection
- Insulin ELISA KIT and its proper storage
- Estimation of serum insulin level using DRG insulin kit and glucose level using glucometer
- To evaluate the role of circadian rhythm on endogenous insulin and glycemic level during day and night cycle
- To assess the relation between serum insulin level and pain in patients with cancer pain patients.

METHODOLGY

6. METHODOLOGY

6.1 Study type:

A Prospective study

6.2 Study site:

Erode cancer centre, Erode

6.3 Sample size:

22 patients

Control group : 6 cancer patients without pain

Group A : 8 cancer patients undergoing opioid treatment

Group B : 8 cancer patients undergoing Nonopioid treatment

6.4 Study Duration:

8 months

6.5 Ethical clearance:

Ethical committee clearance approval were granted for this study by the institutional ethical committee (IEC),Swami Vivekananda college of pharmacy to carry out this work.

6.6 Patient selection:

Inclusion criteria:

- Study population includes cancer patients undergoing opioid and nonopioid treatment and cancer patients without pain(control group)
- Age 30-70 years

Exclusion criteria:

- Patients were excluded,
- If they are unable to comply with protocol requirements
- Patient with diabetes,hyperlipidemia,cardiovascular complications, liver and renal dysfunction
- Patients taking corticosteroids.

6.7 Patient data entry form:

Patient data entry form included patient details such as name, age, sex ,height, weight, bodymassindex, education, occupation, past medical history, past medication history, family history, social history, dietary habits, type of cancer, stage of cancer, site of pain, VAS score, treatment regimen for both cancer and pain

6.8 Blood sample collection:

5 ml of peripheral venous blood was collected by vein puncture using a dry disposable syringe

- Approximately 5ml each 4 times a day
- Morning :6 am
- Afternoon :12 pm
- Evening :6 pm
- Midnight :12 am

6.9 Parameters to be investigated:

All the cases, control, cancer patients with pain and cancer patients without pain will be considered for the investigation of **insulin** and **glucose** level.

6.10 Estimation of glucose levels:

Glucose levels were estimated using glucometer (Accue Sure, Microgene Diagnostic systems Pvt. Ltd., New Delhi). A drop of blood was collected and placed on glucometer strip. The values of glucose levels, as indicated in the display screen, were recorded.

6.11 Estimation of serum insulin:

Serum insulin level was estimated by ELISA method by using DRG INSULIN KIT .

Name and intended use: The **DRG Insulin Enzyme Immunoassay Kit** provides materials for the quantitative determination of insulin in serum and plasma. This assay is intended for in vitro diagnostic use only.

Insulin is the principal hormone responsible for the control of glucose metabolism .it is synthesized in the β-cells of the islets of Langerhans as the precursor, proinsulin,which is processed to form c-peptide and insulin. both are secreted in equimolar amounts into the portal circulation. the mature insulin molecule comprises 2 polypeptide chains, the A chain and B chain(21 and 30 amino acids respectively).the 2 chains are linked together by 2 inter-chain disulphide bridges. There is also an intra-chain disulphide bridge in the A chain.

Secretion of insulin is mainly controlled by plasma glucose concentration, and the hormone has a number of important metabolic actions. its principal function is to control the uptake and utilization of glucose in peripheral tissues via the glucose transporter. This and other hypoglycemic activities, such as the inhibition of hepatic gluconeogenesis and glycogenolysis are counteracted by the hyperglycemic hormones including glucagon, epinephrine (adrenaline), growth hormone and cortisol.

Insulin concentrations are severely reduced in insulin-dependent diabetes mellitus(IDDM) and some other conditions such as hypopituitarism.insulin levels are raised in non-insulin dependent diabetes mellitus(NIDDM),obesity, insulinoma, and some endocrine dysfunctions such as Cushing's syndrome and acromegaly.

PRINCIPLE OF THE TEST:

The DRG insulin ELISA kit is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. The micro titer wells are coated with a monoclonal antibody directed towards a unique antigenic site on the insulin molecule. An aliquot of patient sample containing endogenous insulin is incubated in the coated well with enzyme conjugate, which is an anti-insulin antibody conjugated with Biotin. After incubation the unbound conjugate is washed off. During the second incubation step Streptavidin Peroxidase Enzyme Complex binds to the biotin- anti –insulin antibody. The amount of bound HRP complex is proportional to the concentration of insulin in the sample. Having added the substrate solution, the intensity of colour developed is proportional to the concentration of insulin in the patient sample.

Kit components:

Content of the kit:

1. Micro titer wells,12×8 strips, 96 wells .Wells coated with anti insulin monoclonal antibody
2. Zero standard, 1 vials, 3ml, ready to use
3. Standard (standard1-5), 5 vials, 1ml, ready to use,

   Concentrations: 6.25-12.5-25-50and 100µLu/ml

4. Enzyme Conjugate,1vial,5 ml, ready to use, mouse monoclonal anti insulin conjugated to biotin
5. Enzyme Complex,1 vial,7 ml, ready to use, Streptavidin HRP complex
6. Substrate solution ,1 vial,14 ml, ready to use,TMB

7. Stop Solution,1 vial,14 ml, ready to use, contains 0.5M H_2SO_4
8. Wash Solution,1 vial,30 ml(40×concentrated)

Equipment and material required but not provided

- A micro titer plate calibrated reader(450±10nm)
- Calibrated variable precision micropipettes
- Absorbent paper
- Aqua dest.

Storage and stability of the kit:

When stored at 2-8 c unopened reagents will retain reactivity until expiration date. All opened reagents and micro titer wells must be stored at 2-8^c.Once the foil bag has been opened ,care should be taken to close it tightly again.

Preparation of reagents:

Allow all reagents and required number of strips to reach room temperature prior to use.

Wash solution:

Dilute 30 ml of concentrated wash solution with 1170 ml deionized water to a final volume of 1200 ml.The diluted wash solution is stable for 2 weeks at room temperature.

Specimen collection:

Serum or plasma can be used in this assay. Serum is used here

SERUM: collect blood by venipuncture, allow to clot, and separate serum by centrifugation at room temperature.

A**ssay procedure:**

- Secure the desired number of micro titer wells in the holder

- Dispense 25µl of each standard,controls,and samples with new disposable tips into appropriate wells
- Dispense 25µl enzyme conjugate into each well
- Thoroughly mix for 10 seconds. it is important to have a complete mixing in this step
- Incubate for 30 minutes at room temperature without covering the plate
- Briskly shake out the contents of the wells. rinse the wells 3 times with diluted wash solution. strike the wells sharply on adsorbent paper to remove residual droplets
- Add 50µl of enzyme complex to each well
- Incubate for 30 minutes at room temperature
- Briskly shake out contents of the wells. Rinse the well 3 times with diluted wash solution. Strike the wells sharply on adsorbent paper to remove residual droplets
- Add 50µl of substrate solution to each well
- Incubate for 15 minutes at room temperature
- Stop the enzymatic reaction by adding 50µl of stop solution to each well
- Read the OD at 450±10 nm with a micro titer plate reader within 10 minutes after adding the stop solution.

RESULTS

7. RESULTS

Chronological influence on insulin level and glycemic status is a prospective case control study done in Erode Cancer centre, Erode. This study was carried out for a period of 9 months. Out of 50 patients screened we recruited 22 patients for this study whose age ranged from 30- 70 years. The study protocol was approved by the Institutional Research Ethical Committee of Swamy Vivekananda College of pharmacy and granted permission for the conduct of study.

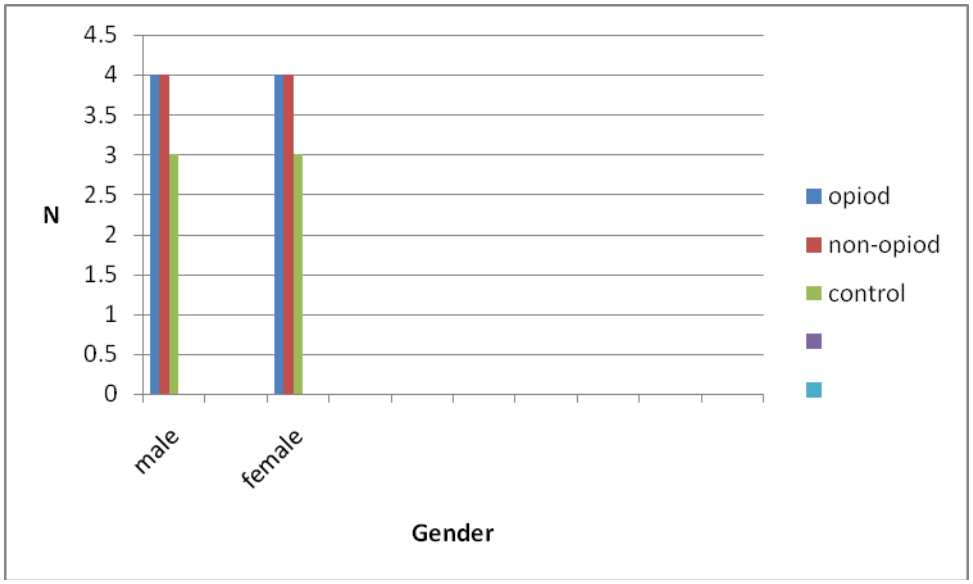
Patients were categorized as Group A, Group B, Group C for the study. Group A included 8 patients taking opiod drugs, Group B included 8 patient taking nonopiod drugs and Group C included 6 control patients without pain. Patient with diabetes, hyperlipidemia, cardiovascular complications, liver and renal failure, Patients taking corticosteroids were excluded from the study. Patient data entry format was prepared to record patients' demographic details, past medical and medication history, family history and pain score. Pain was assessed in patients using Visual Analogue Scale. Blood samples were collected from patients four times a day(12PM,6PM,12AM,6AM)with their consent. Biochemical parameters such as insulin and glucose levels were estimated. Serum Insulin level were determined by ELISA method using DRG INSULIN KIT. Glucose levels were estimated using glucometer.

7.1 DEMOGRAPHIC DETAILS:

7.1.1. Gender distribution:

All the patients included for the study were divided into opioid , nonopioid and control group. In control group,3 males and 3 females were present. Opioid group included 4 male patients and 4 female patients. And in nonopioid group 4 males and 4 females were present. Amongst 22 participants in the study (11) 50% were males and (11) 50% were females.

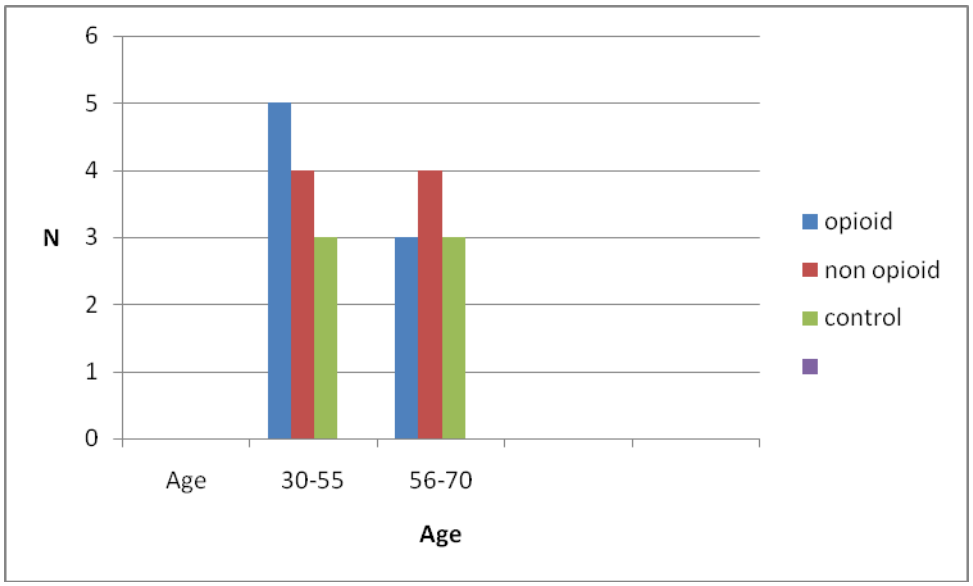
Figure 1 .Gender distribution for different groups of study population



7.1.2.Age distribution:

Age distribution showed that (12) 54.5%were in 30-55 age group, (10) 45.4% were in 56-70 age group .In opioid group 5 males(62%) and 3 females(37.5)were present. In nonopioid group 4(50%) males and 4(50) females and in control group 3 males(50%) and 3 female(50%) patients present.

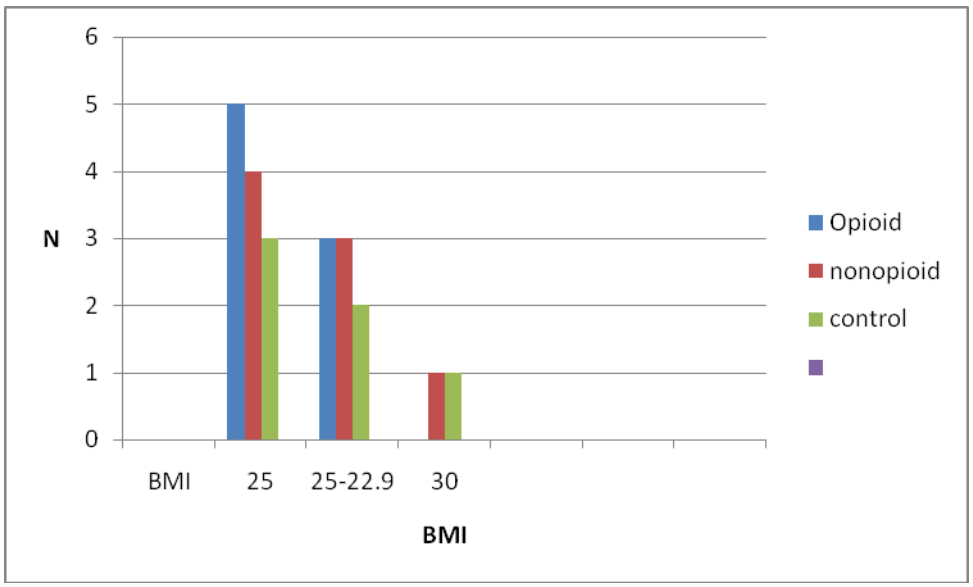
Fig 2. Age distribution for different groups of study population



7.1.3.BMI profile:

Among 8 patients in opioid group, 5(62.5%)were normal weight, 37.5% were overweight. Among 8 patients in nonopioid group, 4(50%) were normal weight, 3(37.5%) were overweight and 1(12.5%) were obese. In control group 3(50%) were of normal weight 2(33.3%) were overweight and 1(16.65%0 were obese. Out of the total participants in the study 9(40.9%) were normal weight,11(50%) were overweight and 2(9.09%) obese.

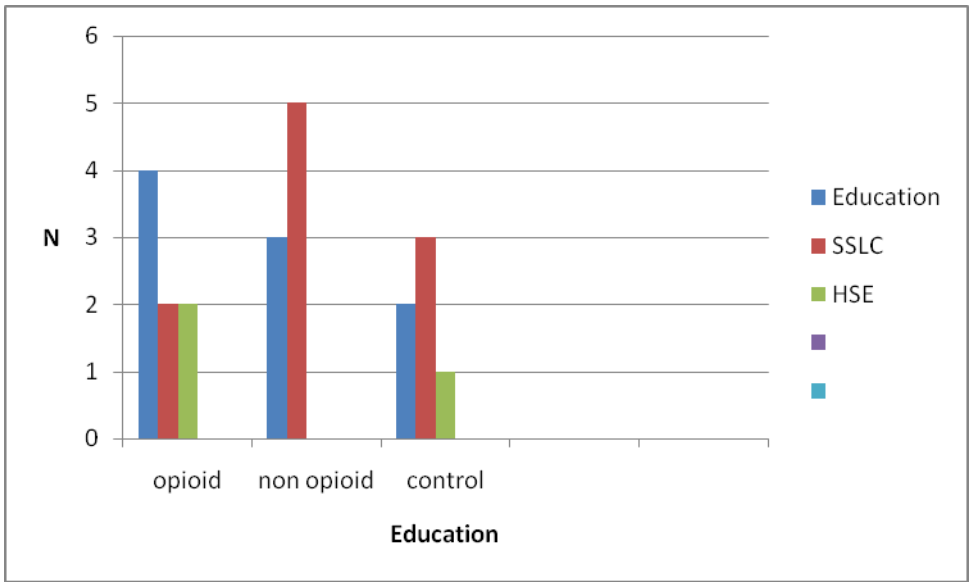
Fig 3. BMI distribution for different groups of study population



7.1.4. Education status:

Out of the total 22 participants in the study group, analysis of their education level indicate that (9)40.9% individual completed SSLC,(10)45.4% had secondary school level education,(3) 13.6%individual were graduates.

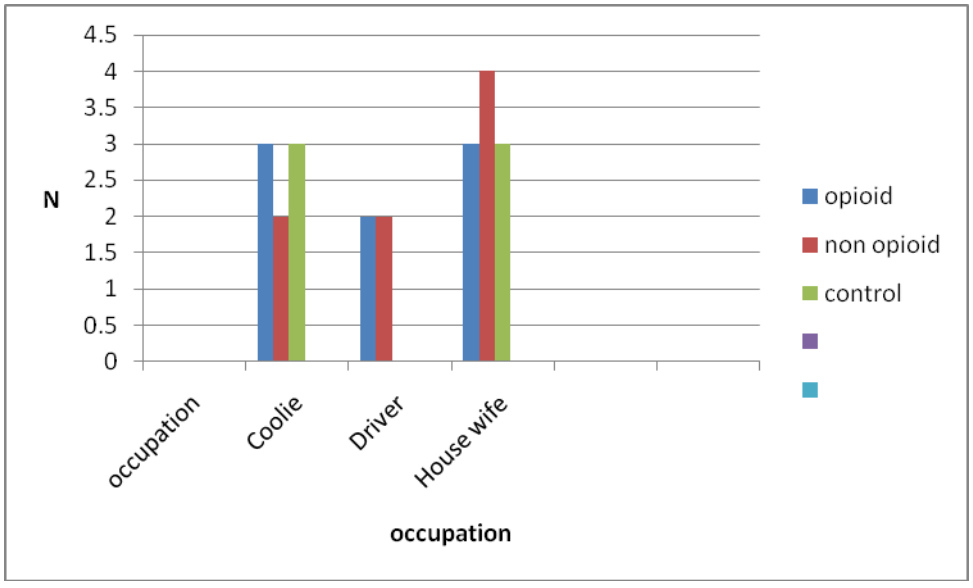
Fig 4. Education level for different groups of study population



7.1.5. Occupation profile of study population

Amongst the 22 patients (8) 36.3% were coolie,(4) 18.8% were drivers,(10) 45.4% were house wife.

Fig: 5. Occupation level for different groups of study population



7.1.6. Social history profile for different groups of study participants

Among 22 patients in the study (8)31.8% were smokers,(14)63.6% were non-smokers,(8) 36.3% were alcoholics ,(14)63.6% were non alcoholics

Fig: 6. Social history for different groups of study population

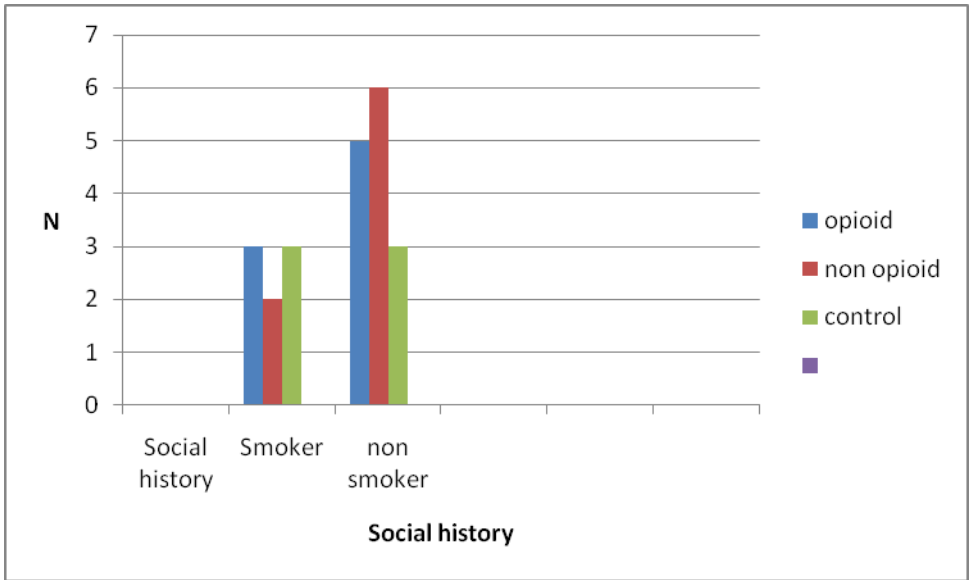


Table 1. Demographic details of study group

Parameter	Number of subject (%)			
	Opioid (N=8)	Non opioid (N=8)	Controls (N=6)	Total (N=22)
Sex				
Men	4(50%)	4(50%)	3(50%)	11(50%)
Women	4(50%)	4(50%)	3(50%)	11(50%)
Age				
30-55	5(62%)	4(50%)	3(50%)	12(54.5%)
56-70	3(37.5%)	4(50%)	3(50%)	10(45.4%)
BMI				
25	5(62.5%)	4(50%)	3(50%)	9(40.9%)
25-29.9	3(37.5%)	3(37.5%)	2(33.3%)	11(50%)
30	0(0%)	1(12.5%)	1(16.65%)	2(9.09%)
Education status				
Lliterature				
SSLC	4(50%)	3(37.5%)	2(33.3%)	9(40.9%)
HSE	2(25%)	5(62%)	3(50%)	10(45.4%)
UG	2(25%)	-	1(16.6%)	3(13.6%)
Occupation				
Coolie	3(37.5%)	2(25%)	3(50%)	8(36.3%)
Driver	2(25%)	2(25%)	-	4(18.8%)
House wife	3(37.5%)	4(50%)	3(50%)	10(45.45%)
Smoking History				
Smoker	3(37.5%)	2(25%)	3(50%)	8(36.3%)

Non-smoker	5(62.5%)	6(75%)	3(50%)	14(63.6%)
Alcoholism				
Yes	3(37.5%)	2(25%)	3(50%)	8(36.3%)
No	5(62.5%)	6(75%)	3(50%)	14(63.6%)

7.2)Classification of study participants based on type of cancer

Out of 22cancer patients in the study, most of them were suffering from cervical cancer (3)13.6%,breast cancer (3)13.6% and cancer of oral(4)18.8%.In this group of patients most of them were prescribed with opioid drugs which indicated they suffered severe pain.(3) 13.6%were suffering from cancer of stomach and oesophagus and neck cancer.1(4.05%) was suffering from cancer of ovary and uterus The remaining (2)9.09% patients were categorized as other type of cancer which included cancer of lungs and peripheral nerve sheeth tumor.

Table 2.Classification of Cancer

SL NO	TYPES OF CANCER	No; in total groups in %
1	Cancer of Cervix	3(13.6%)
2	Cancer of Breast	3(13.6%)
3	Oral Cancer	4(18.8%)
4	Esophagus cancer	3(13.6%)
5	Stomach cancer	3(13.6%)
6	Neck cancer	3(13.6%)
7	Other types of cancer	2(4.05%)

Results were analyzed using computerized statistical package of Graph pad Instat software. The statistical significance was tested by the analysis of variance (ANOVA) and Tukey - Kramer Multiple Comparisons Test. All data are presented as mean ± SD(SEM)

7.3) Effect of circadian rhythm on serum insulin level

7.3.1) Effect of circadian rhythm on serum insulin level in opioid,nonopiod and control group at 6AM:

The results of the effect of circadian rhythm on serum insulin level at 6AM were shown in Table 3 and Figure 7 . The mean serum insulin level in the control group of patients at 6AM was8±2.315 which was changed in nonopioid group to17.5875±2.847 and 31.3125±7.358 in opioid group. However at 6AM p value was found statistically significant between the three groups.

Table.3 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 6AM

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Serum insulin level in μIU/ml Mean±SD(SEM)	31.3125±20.812 (7.358)	17.5875±8.053 (2.847)	8±5.671 (2.315)	P=0.O176*

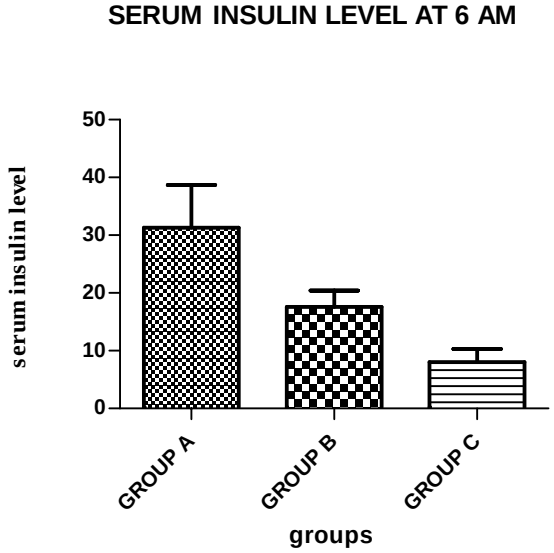


Figure.7 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 6AM**.** n=22; the values are expressed as mean ±SD(SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

Tukey-Kramer Multiple Comparisons Test

opioid vs nonopioid	ns P>0.05
opioid vs control	* P<0.05
nonopioid vs control	ns P>0.05

Table 3. Shows the serum insulin level in the control, opioid, nonopioid taking groups. Extremely significant level of insulin level is seen in both opioid and non-opioid taking patient

group as compared to control group. Serum insulin level is found to be higher in opioid taking group when seen with nonopioid groups which may be due to high pain level in opioid taking patients.

7.3.2) Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 12PM:

The results of the effect of circadian rhythm on serum insulin level at 12PM were shown in Table 4 and Figure 8.The mean serum insulin level in the control group of patients at 12noon was 7.4±2.584 which was changed in nonopioid group to 18.3625±3.087 and 33.05±4.510 in opioid group. However at 12PM p value was found statistically significant between the three groups.

Table.4 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 12PM

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Serum insulin level in μIU/ml Mean±SD(SEM)	33.05±12.757 (4.510)	18.3625±8.731 (3.087)	7.4±6.331 (2.584)	P=0.0005***

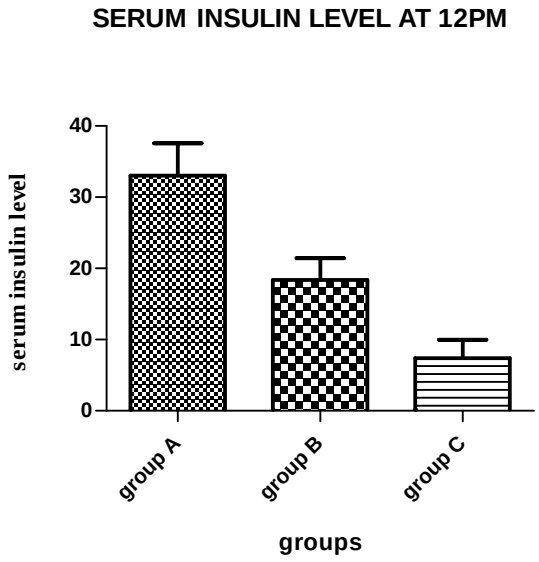


Figure.8 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 12PM**.** n=22; the values are expressed as mean ±SD(SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

Tukey-Kramer Multiple Comparisons Test

opioid vs non opioid	* P< 0.05
opioid vs control	*** P<0.001
nonopioid vs control	ns P>0.05

This shows that serum insulin level is found to be higher in opioid taking group when compared with Nonopioid group due to high pain level in this group.

7.3.3) Effect of circadian rhythm on serum insulin level in opioid,nonopiod and control group at 6PM:

The results of the effect of circadian rhythm on serum insulin level at 6PM were shown in Table 5 and Figure 9. The mean serum insulin level in the control group of patients at 6PM was 5.483±1.511 which was changed in nonopioid group to 69.1875±7.527 and13.7875±1.431 in opioid group. However at 6PM p value was found statistically significant between the three groups.

Table.5 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 6PM

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Serum insulin level in μIU/ml Mean±SD(SEM)	13.7875±4.047 (1.431)	69.1875±21.290 (7.527)	5.483±3.702 (1.511)	P=0.0001***

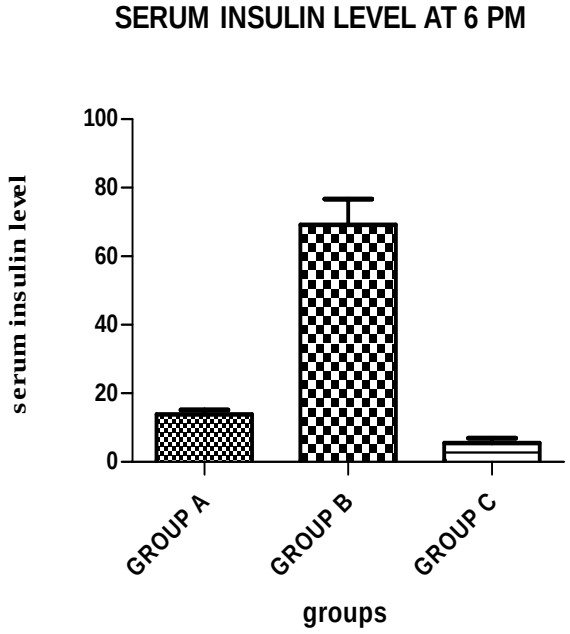


Figure.9 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 6PM**.** n=22; the values are expressed as mean ±SD(SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

Tukey-Kramer Multiple Comparisons Test

opioid vs nonopioid	*** P<0.001
opioid vs control	ns P>0.05
nonopioid vs control	*** P<0.001

Table 5. shows the serum insulin level in the control, opioid,nonopioid taking groups. Extremely significant level of insulin level is seen in both opioid and non-opioid taking patient group as compared to control group. Serum insulin level is found to be higher in nonopioid taking group when seen with opioid groups.

7.3.4) Effect of circadian rhythm on serum insulin level in opioid,nonopiod and control group at 12AM:

The results of the effect of circadian rhythm on serum insulin level at 12AM were shown in Table 6 and Figure 10. The mean serum insulin level in the control group of patients at 12AM was 5.6333±1.568 which was changed in nonopioid group to 67.3375±10.864 and 10.325±1.761 in opioid group. However at 12AM pvalue was found statistically significant between the three groups.

Table .6 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 12AM

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Serum insulin level in μIU/ml Mean±SD(SEM)	10.325±4.980 (1.761)	67.3375±30.728 (10.864)	5.6333±3.842 (1.568)	P<0.0001***

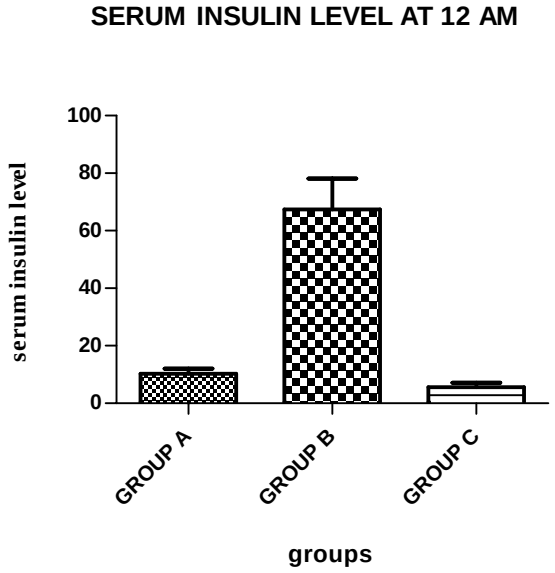


Figure.10 Effect of circadian rhythm on serum insulin level in opioid,nonopioid and control group at 12AM**.** n=22; the values are expressed as mean ±SD (SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

Tukey-Kramer Multiple Comparisons Test

opioid vs nonopioid	*** P<0.001
opioid vs control	ns P>0.05
nonopioid vs control	*** P<0.001

Table 6. shows the serum insulin level in the control, opioid,nonopioid taking groups. Extremely significant level of insulin level is seen in both opioid and non-opioid taking patient group as

compared to control group. Serum insulin level is found to be higher in nonopioid taking group when seen with opioid groups .This may be due to high pain level in nonopioid taking patients. This result shows that insulin level is increased at midnight in nonopioid taking patients From this understand that circadian rhythm influence on pain.

The results of the above data is in concordance with the findings of Nitya et al(2010),wherein reported relation between pain and insulin level is observed in cancer pain patients whereas no change in the glucose levels. The results also coincides with the finding that insulin possess antinociceptive action and this antinociceptive effect could be due to hypoglycemia and release of endogenous opioid peptides ;Takeshita et al.Another preclinical study reported insulin is involved in the modulation of pain in animal. Serum insulin showed a significant rise whenever antinociceptive response was recorded irrespective of glycemic state;Rajendran et al(2001).The results of the study also coincides with the finding of Jacob et al;stated that acute severe pain decreases insulin sensitivity. So the mechanism of action may be due to the development of insulin resistance. These results thereby reveals that in painful condition like cancer pain increased levels of insulin levels were observed when compared with control group.

7.4) Effect of circadian rhythm on blood glucose level:

7.4.1) Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 6AM:

The results of the effect of circadian rhythm on blood glucose level at 6AM were shown in Table 7 and Figure 11. The mean blood glucose level in the control group of patients at 6AM was 88.666±5.925 which was changed in nonopioid group to87.25±3.353 and 85.125±3.287 in opioid group However, these increase were statistically not significant (P>0.05).

Table.7 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 6AM.

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Blood glucose level in mg/dl Mean±SD(SEM)	85.125±9.296 (3.287)	87.25±9.483 (3.353)	88.666±14.514 (5.925)	P=0.8315 NS

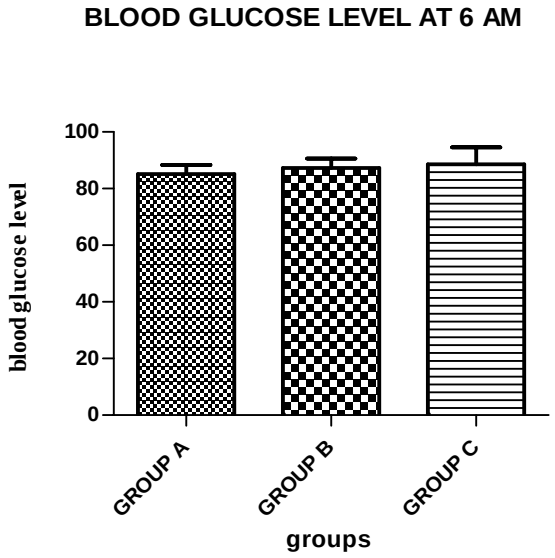


Figure.11 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 6AM**.** n=22; the values are expressed as mean ±SD(SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

The above data reveals that, there was no statistical significant relationship between changes in blood glucose level ($p>0.05$) in control, opioid taking and nonopioid taking groups in cancer patients.

7.4.2) Effect of circadian rhythm on blood glucose level in opioid,nonopiod and control group at 12PM:

The results of the effect of circadian rhythm on blood glucose level at 12PM were shown in Table 8 and Figure 12. The mean blood glucose level in the control group of patients at 12PM was 88.166±5.300 which was changed in nonopioid group to 86.5±2.471 and 84.625±3.545 in opioid group However, these increase were statistically not significant (P>0.05).

Table.8 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 12PM.

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Blood glucose level in mg/dl Mean±SD(SEM)	84.625±10.028 (3.545)	86.5±6.990 (2.471)	88.166±12.983 (5.300)	P=0.8049 NS

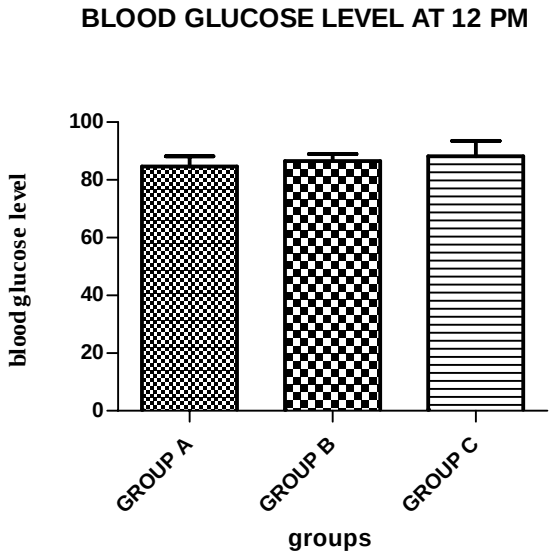


Figure.12 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 12PM**.** n=22; the values are expressed as mean ±SD(SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

7.4.3) Effect of circadian rhythm on blood glucose level in opioid,nonopiod and control group at 6PM:

The results of the effect of circadian rhythm on blood glucose level at 6PM were shown in table 9 and figure 13. The mean blood glucose level in the control group of patients at 6PM was 88±3.830 which was changed in nonopioid group to 86.625±2.521 and 87.25±3.427 in opioid group However, these increase were statistically not significant (P>0.05).

Table.9 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 6PM.

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Blood glucose level in mg/dl Mean±SD(SEM)	87.25±9.692 (3.427)	86.625±7.130 (2.521)	88±9.381 (3.830)	P=0.9586 NS

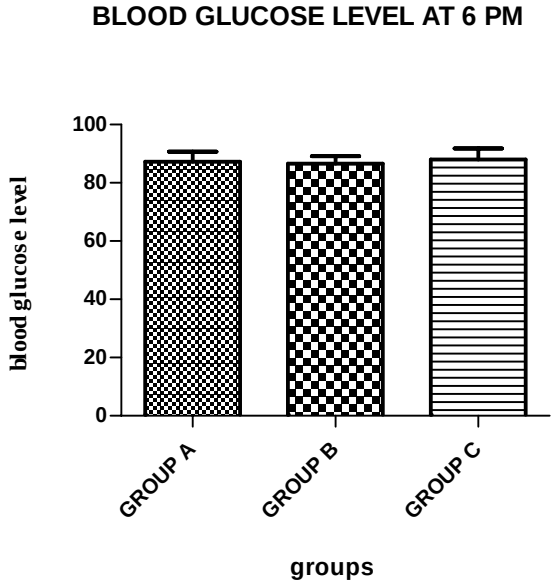


Figure.13 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 6PM**.** n=22; the values are expressed as mean ±SD(SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

7.4.4) Effect of circadian rhythm on blood glucose level in opioid,nonopiod and control group at 12AM:

The results of the effect of circadian rhythm on blood glucose level at 12AM were shown in Table 10 and Figure 14. The mean blood glucose level in the control group of patients at 12AM was 86.5±4.023 which was changed in nonopioid group to 85.25±2.610 and 83.625±3.262 in opioid group However, these increase were statistically not significant (P>0.05).

Table.10 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 12AM.

PARAMETER	OPIOID (n=8)	NONOPIOID (n=8)	CONTROL (n=6)	P VALUE
Blood glucose level in mg/dl Mean±SD(SEM)	83.625±9.226 (3.262)	85.25±7.382 (2.610)	86.5±9.854 (4.023)	P=0.8292 NS

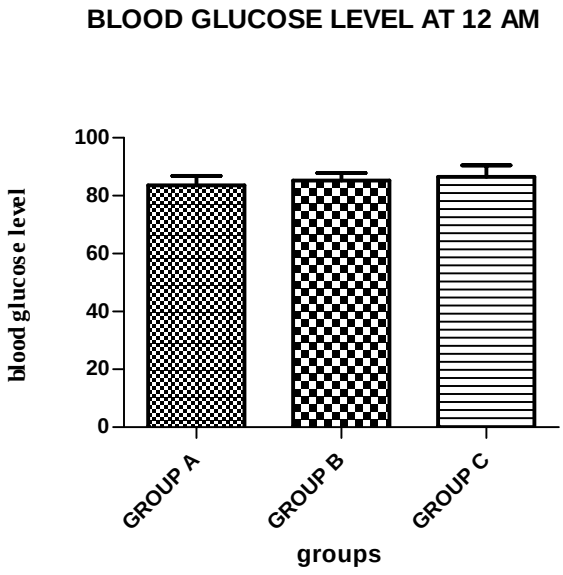


Figure.14 Effect of circadian rhythm on blood glucose level in opioid,nonopioid and control group at 12AM**.** n=22; the values are expressed as mean ±SD(SEM); (one way ANOVA followed by Tukey's multiple comparison Test)

The above data reveals that,there was no statistical significant relationship between changes in blood glucose level($p>0.05$) in control, opioid taking and nonopioid taking groups in cancer patients.

The results of this study is in adherence with the findings of Nitya et al(2010),wherein reported relation between pain and insulin level in cancer patients independent of the glucose levels. Another preclinical study reported that serum insulin showed a significant rise whenever antinociceptive response was recorded irrespective of glycemic state Rajendran et al(2001).The results also coincides with the finding that an i.c.v injection of insulin dose dependently attenuated the formalin induced antinociception, but it did not lower the blood glucose level even at the largest dose.T he results of this study coincides with these findings.

Table 11.Influence of time on serum insulin level in cancer patients .

PARAMETER	OPIOIDS		NONOPIOIDS	
	12PM	6AM	6PM	12AM
Serum insulin level in µIU/ml Mean±SD(SEM)	33.05±12.757 (4.510)	31.3125±20.812 (7.358)	69.1875±21.290 (7.527)	67.3375±30.728 (10.864)

In opioid taking group, serum insulin level showed an increase at 12pm and 6 am whereas in nonopioid taking group rise in insulin level was seen at 6pm and 12am.This clearly indicates that circadian rhythm shows a great influence in the insulin release

Table 12. Influence of gender on insulin level in opioid taking cancer patients

GENDER	6AM	12PM	6PM	12AM
MALE	34.575	32.075	12.175	11.925
FEMALE	30.05	34.025	15.4	8.75

Table 13.Influence of gender on insulin level in nonopioid taking cancer patients

GENDER	6AM	12PM	6PM	12AM
MALE	20.725	20.975	76.5	73.457
FEMALE	17.45	19.75	71.875	69.2

There was no significant difference in insulin levels among both genders in opioid and nonopioid cancer patients.

DISCUSSION

8. DISCUSSION

The results of this study clearly demonstrates that endogenous insulin is involved in the modulation of pain in different types of cancer and this is influenced by circadian rhythm.

A circadian rhythm is an endogenously driven roughly 24-hour cycle in biochemical, physiological, or behavioral processes. It is cell-autonomous. The information of the time of the day as relayed by the eyes travels to the clock in the brain, and, through that, clocks in the rest of the body may be synchronized. This is how the timing of, for example, sleep/wake, body temperature, and thirst, and appetite, periodic release of hormones are coordinately controlled by the biological clock. Circadian rhythm is linked to the light–dark cycle. Animals, including humans, kept in total darkness for extended periods eventually function with a free running rhythm. Each "day", their sleep cycle is pushed back or forward, depending on whether their endogenous period is shorter or longer than 24 hours. The environmental cues that reset the rhythms each day are called zeitgebers .The SCN (Suprachiasmatic Nucleus) is the central pacemaker capable of synchronizing the cellular rhythms to produce observable circadian rhythms[58,59] .

Most people experience pain in one way or other and take analgesics or pain killers to alleviate the pain. However the intensity of pain varies with times and this has been observed in much clinical painful condition. For example, pain in rheumatoid arthritis occurs mostly at the beginning of the day. The reason for high pain intensity is due to high production of cytokines during early morning and also plasma cortisol (anti-inflammatory) is lowest and melatonin (proinflammatory) is highest during this timings (Cutolo M et al)[72] and thus clearly signals the influence of circadian rhythm on the modulation of pain over time.

The involvement of endogenous insulin in the modulation of pain both in animals (Rajendran et al)[21] and humans(Nitya et al)[17] has been well documented. Circadian rhythm

variations show changes in insulin level, as evidenced in animals or humans. As endogenous insulin has been implicated in the modulation of pain and also stated that it is influenced by circadian rhythm, the pain perception at different time is obvious.

Of the several painful clinical condition, cancer pain management remains a challenge and the mechanism underlying this is not clearly established. Previously it has been reported that there exists a relation between cancer pain and endogenous insulin (Nitya et al)[17].However whether circadian rhythm influences such a relationship is not established and therefore the present study aimed to investigate the relation between endogenous insulin and pain in different cancers and also the influence of circadian rhythm on the relation between endogenous insulin and cancer pain.

Earlier studies revealed that insulin produces analgesic response independent of the glycemic status(Takeshita et al)[19] and the analgesic response was mediated through 5-HT,dopamine,NMDA and opioid peptides and also potassium and calcium channels(Anuradha et al)[18].Thus studies so far conducted established the relationship between endogenous insulin level and pain threshold independent of glycemic status.

In this study it was observed, significant increase in endogenous insulin levels in both opioid and nonopioid group as compared to control in cancer pain patients and the effect was independent of the glycemic status. These findings are inconsistent with earlier reports that high endogenous insulin level was observed in patients with pain in neck, shoulder and back(Elizabeth et al)[37].The same fact was observed in another study wherein both opioid and nonopioid drugs caused a significant increase in endogenous insulin in patients with cancer pain and the endogenous insulin was not associated with glycemic status(Nitya et al)[17].

The effect of circadian rhythm on the endogenous insulin in cancer pain patients receiving opioid or nonopioid analgesics was also examined. The cancer pain patients who received who received opioid group showed a significant increase in endogenous insulin level in day cycle(6am and 12pm) whereas in nonopioid group showed significant increase in endogenous insulin level in night cycle(6pm and 12'oclock midnight).

On subjective analysis of cancer patients it was found, opioid group patients report more severity of pain in the day time than in the night time and therefore it is obvious

from our study, the changes in endogenous insulin level, high in day time an low in the night time.Besides,as a normal physiological function pancreas secrete more insulin in daytime and less in the night time in humans. These factors support our findings that circadian rhythm has a role to play in the endogenous insulin level relative to the intensity of pain.

On comparison of insulin level between opioid and nonopioid groups there was about 2 fold increase in endogenous insulin level in nonopioid group and the mechanism underlying this is not clearly understood. Endogenous insulin has so far been implicated in the modulation of opioid mediate pain in the studies so far conducted and our finding with respect to two fold increase in insulin level in nonopioid group is surprising which need to be addressed in detail.

We hypothesize the following factors may be reason for elevated endogenous insulin level in nonopioid group compared to opioid group. It has been stated that bradykinin stimulated insulin release (Chi yang et al)[76]. Bradykinin play a significant role in acute and chronic inflammatory pain.Bradykinin influences many biological processes such as blood pressure, local blood flow, pain and inflammation. Bradykinin activity is mediated by 2 receptors, namely B1 and B2 receptors. The effects attributed to kinins are mainly mediated by B2 receptor which is expressed in many organs under physiological conditions. Conversely, B1receptor is present only in low concentration in most tissues, but inflammation and pain triggers a strong up-regulation of B1 receptor expression in different organs(Molly A .Sevcik et al)[79]. Leptin is an adipocytokine that shows broad effects on energy balance, inflammation and vascular tone. Insulin is one of the major physiological and positive regulators of leptin expression and secretion in rodents and humans.B1 receptor is expressed in painful stimuli and this receptor causes leptin release which showed subsequent increase in insulin level.(Marcelo A Mori et al)[75].

Bradykinin showed insulin sensitivity via activation of B2 receptors whereas B1 receptor may participate in this process through a cross walk with B2 receptor subtype addressed in a study(Leeb Lundberg LM et al)[77].A study reports that cytokines such as tumor necrosis factor α and interleukin -1 promote strong over expression of both leptin and kinin B1 receptor

mRNAs(Grunfeld C)[78].Therefore it is strongly evident that pain causes release of cytokines and bradykinin.These two inturn results in βcell contraction causing an increase in insulin.

Thus, the present study explores the possible role of endogenous insulin in cancer pain and also the circadian rhythm influences the endogenous insulin level in cancer pain patients particularly receiving opioid analgesics. Though cytokines and bradykinin may be contributing to endogenous insulin level in nonopioid group of patients a detailed study is warranted to clearly address this issue.

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

- VAS scale is an effective tool in assessing pain score in cancer pain.
- Endogenous insulin is involved in the modulation of pain.
- In painful condition like cancer pain, insulin possessed antinociceptive action with rise in endogenous insulin level independent of the glycemic status.
- Circadian rhythm plays an important role on endogenous insulin in cancer pain.
- Significant increase in insulin was observed in opioid group at the day cycle whereas in the nonopioid group the same effect was observed in the night cycle. This shows the influence of circadian rhythm over the insulin release.
- Thus, it can be concluded that endogenous insulin plays a role in the modulation of cancer pain treated by opioid and nonopioid analgesics and the circadian rhythm influences the relation between endogenous insulin and cancer pain.
- A detailed study in a larger population would help to understand the mechanism of endogenous insulin in clinical painful conditions and how they are affected by circadian rhythm.

FUTURE PLAN

10. FUTURE PLAN

Further studies are required in more number of subjects to confirm the influence of circadian rhythm on insulin level and glycemic status in cancer pain patients.

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ANNEXURES

DATA ENTRY FORM

PATIENT DETAILS

NAME: **AGE:**

SEX: **BMI :**

PAST MEDICATION HISTORY:

FAMILY HISTORY:

SOCIAL HISTORY:

SMOKER(Y/N) : **ALCOHILIC(Y/N):**

REASON FOR ADMISSION:

TYPE OF CANCE:

STAGE OF CANCER :

HISTO PATHOLOGICAL DETAILS:

INVESTIGATION :

CHEMOTHERAPY

DRUG :

DOSE:

ROUTE :

HOW MANY CYCLE COMPLETED :

YET TO BE COMPLETED :

TRETMENT OUTCOME:

PAIN SCORE :

<u>LABORATORY INVESTIGATION</u>

SERUM INSULIN LEVEL:

BLOOD GLUCOSE LEVEL:

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

Elayampalayam, Tiruchengode-637 205, Tamilnadu.

PATIENT INFORMATION FORM

STUDY TITLE:

Chronological effect on insulin level and glycemic status in cancer pain patients

STUDY SITE:

Erode Cancer centre, Erode

DESCRIPTION:

This study conducted by NEENU B NIRAVATH [II M.Pharm (Pharmacy Practice), Swamy Vivekanandha College of Pharmacy ,Elayampalayam Thiruchengode-637 205, Tamilnadu.] will help in understanding the insulin level in cancer patients, and the importance of monitoring insulin and glucose level in patients with cancer for better therapeutic outcome.

PARAMETERS TO BE MEASURED:

- Insulin level
- Glucose level

AMOUNT OF BLOOD NEEDED: 5ml

All the volunteers willing to participate in this research study are requested to sign in the patient consent form.

Swamy Vivekanandha College of Pharmacy

Elayampalayam, Thiruchengode-637 205, Tamilnadu

CONSENT FORM

I Mr/Mrs/Miss..... patient of Dr. K.VELAVAN.MD. RT., Consultant Radiation Oncologist & Cancer Chemotherapist, Erode Cancer Centre ,Erode, hereby declare that I have been told in detail by NEENU B NIRAVATH [II M.Pharm (Pharmacy Practice),Swamy Vivekanandha College of Pharmacy,Elayampalayam]about the study titled, **"**CHRONOLOGICAL EFFECT ON INSULIN LEVEL AND GLYCEMIC STATUS IN CANCER PAIN PATIENTS**"**. I have understood completely and I agree to take part in this research and to donate venous blood samples which will help in acquiring knowledge for the benefit of the mankind.

Signature/thumb impression of Patient

Signature of Pharmacist

Signature of Physician

Date: